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Study the results of Combination therapy with Thalidomide - Dexamethasone in newly diagnosed patients with multiple myeloma

CERTIFICATE

This is to certify that this thesis titled "**Study the results of Combination therapy with Thalidomide-Dexamethasone in newly diagnosed patients with multiple myeloma,**" is a bonafide work of the candidate, Dr. KasiViswanathan. T, during the period from August 2009 to July 2012 in partial fulfilment, towards the award of degree of Doctorate of Medicine (higher specialty) in Clinical Haematology for the examinations to be conducted by the Dr.M.G.R Medical University in August 2012.

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(In the name of God, Most Gracious; Most Merciful)

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CONTENTS

ABSTRACT

Background: The advent of novel agents (IMiDs-Thalidomide and Lenalidomide and Bortezomib) in the therapy of Multiple Myeloma (MM) has resulted in superior response rates and progression free survival (PFS). As there is only meagre data from India, we retrospectively analyzed the role of Thalidomide-Dexamethasone (TD) as initial therapy in newly diagnosed MM.

Aims and Objectives of the study: 1) To retrospectively analyze the response rate, progression free survival (PFS) and overall survival (OS) of newly diagnosed multiple myeloma cases treated with Thalidomide-Dexamethasone (TD) as induction therapy. 2) To analyze impact of Autologous Stem Cell Transplantation (ASCT) and Thalidomide maintenance in prolonging the PFS and OS.

Methodology: All patients newly diagnosed to have MM and initiated on TD as initial therapy in the Department of Haematology, between March 2004 and September 2012 were analyzed.

Results: A total of 242 patients with a median age of 54 yrs (range 21 to 80yrs), with a male: female ratio of 2.5 was initiated on TD. At diagnosis anaemia (Hb <10 g/dl) was seen in 59.1%, bone involvement was seen in 57.4%, renal failure (Sr.Creat ≥ 2mg/dl) was seen in 21.1%, hypercalcemia (Corrected Sr.Calcium ≥ 10.5 mg/dl) was seen in 19.8% and plasmacytoma was seen in 23.6%. One patient with past history of MGUS and 5 patients with solitary plasmacytoma had progressed to MM. The proportion of patients according to the Durie Salmon staging (DSS) in the 242 patients was 12.8%, 35.5% and 51.7% for DSS I, II and III respectively. The proportion of patients according to the ISS categorisation of the 209 patients

was 25.4%, 32.5% and 42.1% for ISS I, II and III respectively. Median number of cycles of TD was 7 (range-1 to 27) and the median dose of Thalidomide was 200mg OD (range-50mg to 400mg OD). The median dose of Dexamethasone was 40 mg OD (Range: 8 – 40 mg OD). Aspirin was given as DVT prophylaxis in 217 patients and one patient received Sintrom as he had deep vein thrombosis (DVT) at diagnosis. One patient was continued on Clopidogrel, which was initiated after a cerebrovascular event in the past. Seventeen patients were excluded for analysis and considered lost to follow up as they did not have response assessment after initiation of TD. The overall response to TD was 80.4%, with a complete response unconfirmed + complete response (CRu+CR) rate of 8.8%, very good partial response (VGPR) rate of 31.1%, partial response (PR) rate of 40.4% and no response (NR) rate of 19.6%. The median time to respond was 3 months (range: 1-13 months). ASCT was done in 29 patients, 13 patients upfront post TD induction and 16 patients after salvage therapy after relapse/progressive disease. Thalidomide maintenance was initiated post response to TD in for 49 patients. In one hundred and nineteen patients responding to TD did not have any further therapy. The progression free survival (PFS) at 36 months in the ASCT group, Thalidomide maintenance group and no treatment group was 83.3%, 55.1% and 14.7% respectively (p=0.0000). However the overall survival (OS) was not statistically significant among these groups. The 3yr The PFS and OS of the entire cohort of patient was 26.3% and 76.9% respectively.

Conclusion: In this first large series from India, comprehensively analyzing outcome of patients with newly diagnosed MM treated with TD, the response to treatment was similar to those reported in the literature from other population. ASCT and Thalidomide maintenance therapy significantly improved the PFS.

Key words: "Multiple Myeloma", "Thalidomide", "Dexamethasone".

Introduction

Multiple myeloma (MM) is a malignant disorder characterized by a single clone of mature plasma cells producing a monoclonal protein.(1) It accounts for 14% of all hematological malignancies.(2) It usually evolves from an asymptomatic stage of monoclonal gamopathy of undetermined significance (MGUS).(3)

Therapy in multiple myeloma is indicated only if there is related organ or tissue impairment (ROTI) in the form of anaemia, renal failure, hypercalcemia or bone lesion caused by the proliferating plasma cells.(4) The therapy of MM has evolved from Melphalan-Prednisolone (MP)(5) in the 1960s to Autologous stem cell transplantation (ASCT) in the 1980s.(6) VAD (Vincristine, Adriamycin and Dexamethasone) replaced MP as induction therapy prior to ASCT, due to the stem cell toxicity of the Melphalan. VAD followed by ASCT remained the standard of care until the advent of the novel agents.(7)(8) The novel agent, such as the immunomodulatory drugs (IMiDs) - Thalidomide and Lenalidomide and the proteosome inhibitor Bortezomib, has markedly impacted the therapy of MM in the last decade.(9) Thalidomide was the first novel agent used in the therapy of relapsed/refractory MM yielding a response rate of about 30%.(10) Subsequently the addition of Dexamethasone to Thalidomide improved the response rates to 50% in relapsed/ refractory disease. This led to a number of phase II studies using Thalidomide and Dexamethasone (TD) as initial therapy for the treatment of newly diagnosed MM. The overall response rate of TD was 65%, which was similar to VAD chemotherapy.(11) With the ease of orally administered therapy and similar efficacy of TD compared to VAD chemotherapy,

which requires a central line for infusion of drugs, has complications related to the line and the hematological toxicity, TD replaced VAD as initial therapy of MM in the early part of the last decade. Thalidomide has also been used as maintenance therapy post induction and post ASCT. There is evidence of progression free survival benefit(12) with In addition Thalidomide maintenance, however there is conflicting data regarding overall survival benefit.(12)(13) Data on long term outcome of TD is not mature and there is no published literature on the use of TD in newly diagnosed MM from India. In this study we retrospectively analyzed the response rates, progression free survival and overall survival of TD in the treatment of newly diagnosed MM and the benefit of Thalidomide maintenance and ASCT post induction.

Review of Literature

Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for approximately 14% of all hematologialc cancers.(2) MM is characterized by terminally differentiated plasma cells, infiltration of the bone marrow by plasma cells, and the presence of a monoclonal Immunoglobulin or Immunoglobulin fragment in the serum and/or urine.(1) It usually is associated with one or more of the following: osteolytic lesions of the bone, anemia, renal failure and hypercalcemia.(14) Myeloma consistently evolves from an asymptomatic stage of clonal plasma cell proliferation termed "monoclonal gammopathy of undetermined significance" (MGUS).(3) MGUS is present in more than 3% of the population above the age of 50 and progresses to myeloma or related malignancy at a rate of 1% per year.(15),(16) A more advanced stage, "smoldering multiple myeloma"(SMM), is clinically recognized in some patients. The risk of SMM progressing to active myeloma is 10% in the first 5 years, which decreases to 3% between 5 - 10 years and 1% between 10 – 20 years.(17)

The estimated incidence of myeloma and death due to myeloma in US in 2010 was 20,180 and 10,650, respectively.(2) The annual incidence of myeloma, age-adjusted to the 2000 US population, is 4.3 per 100 000.(18) In Europe, the incidence of MM is 6.0 per 100,000 per year.(19) The incidence of myeloma was lower(1-2 per 100,000 per year) in Japan and China, similar to the Asians living in US.(2),(20) The annual incidence of myeloma in India is between 1.28 per 100000 per year.(21) The median age at diagnosis is between 60 - 70 years.(19),(22) There is a slight male predominance with 55% of the affected individuals being males.(2) The prevalence of MM is steadily increasing in view of the improvement in therapy over the last

decade.(9)(23) Using the data between the period 1973-2005 from the database of the Surveillance, Epidemiology, and End Results (SEER) Program, the projected 5-and 10-year relative survival expectations of multiple myeloma patients in the US diagnosed between 2006-2010 below 45 years of age is 68.0% and 55.3% respectively. This exceeds the most up-to-date estimates obtained from traditional cohort and period analysis by 15.5 and 7.0 percent units respectively for 5 yr relative survival and by 19.7 and 7.4 percent units respectively for ten-year relative survival.(24)

History

The first description of Multiple myeloma was published in 1844 by Solly.(Figure – 1 and 2) He described a 39 year old female with fatigue and bone pains due to multiple fractures and named the disease as mollities ossium.(25) Mr. Thomas Alexander McBean, 45 years old male was the first best known case of Multiple myeloma.(26) He also had fatigue, multiple fractures and noted that his "body linen was stiffened by his urine." At autopsy bones were soft, brittle, readily fractured and a "gelatiniform substance of a blood-red colour and unctuous feel" was found in the bones. The term 'multiple myeloma' was first introduced by J.von Rustizky in 1873, after finding eight separate tumor masses in the bones at autopsy of a patient. John Dalrymple examined the bone marrow of McBean and gave the first histological description of plasma cells, which were round or oval shaped, 1.5 – 2 times as large as an average blood cell and contained 1 or 2 nuclei and a bright-colored nucleolus. Geschickter and Copeland emphasized the presence of pathologic fractures, urine BJP, anemia, and chronic renal disease in MM based on 412 cases of MM found in the literature from 1848 to 1928.(27)

Though Waldeyer first used the term “plasma cells” in 1875, the accurate description of perinuclear hoff and eccentric nucleus with blocked chromatin in plasma cells was by Ramon Cajal in 1890.(26) Wright demonstrated plasma cells in normal bone marrow and suggested that Myeloma is a neoplasm originating from the plasma cells.(26) Sternal bone-marrow aspiration was reported by Arinkin in 1927 and facilitated the diagnosis of MM.(26)

Thomas Watson, William Macintyre and Bence Jones first described in 1845 the characteristics of the urine protein found in a patient with MM. The addition of nitric acid to the urine produced a precipitate that was re-dissolved on heating and reappeared on cooling. Fleischer was the first to use the term ‘Bence Jones Protein’ in 1880.(26) Two types of BJP were identified using antisera prepared by immunizing rabbits with injection of BJP. Korngold and Lipari demonstrated that antisera to BJP also reacted against myeloma protein and as a tribute to them, the two types of BJP were named kappa and lambda.(28) It was not untill hundred and seventeen years after the first description of urine BJP, Edelman & Gally in 1962 demonstrated that the urine BJP and the light chains prepared from an IgG monoclonal protein of the same patient had an identical amino-acid composition. These light chains precipitated when heated to between 40˚C and 60˚C, dissolved on boiling and re-precipitated with cooling to between 40˚C and 60˚C, which is identical with the heat properties of BJP.(29)

In 1928 Perlzweig et al described hyperproteinemia in MM.(27) Tiselius separated serum proteins into three components and designated them as alpha, beta, and gamma.(30) Tiselius and Kabat demonstrated that the antibody activity resides in the gamma globulin fraction.(31) The characteristic of multiple myeloma, the tall, narrow-based “church spire” peak was recognized in 1939.(32) The moving-field electrophoresis, a cumbersome and a daylong procedure was replaced in 1951 by electrophoresis using filter paper as a support.(33) Cellulose acetate replaced

filter paper and currently agarose gel or capillary electrophoresis is used for serum and urine protein electrophoresis. In 1953 Grabar and Williams described Immunoelectrophoresis (34) and 11 years later, Wilson introduced immunofixation electrophoresis.(35)

Jan Waldenstrom introduced the concept of monoclonal vs. polyclonal gammopathies in 1961.(36) He considered the broad band in hypergammaglobulinemia as a polyclonal increase in globulins. It is important to distinguish monoclonal from polyclonal gammopathies, because patients with a monoclonal gammopathy either have a neoplastic process or may develop a malignancy subsequently. Many of his patients had multiple myeloma or macroglobulinemia, while others had no evidence of malignancy and he considered them to have "essential hypergammaglobulinemia" or a "benign monoclonal protein". With our present understanding of plasma cell dyscrasias, the preferred terminology today is Monoclonal Gammopathy of Undetermined Significance (MGUS), as multiple myeloma, macroglobulinemia, light-chain (AL) amyloidosis, or a related disorder may subsequently ensue.(15)

Any protein that migrated to the γ mobility region in the electrophoretic pattern was termed `gamma globulin' and are now referred to as immunoglobulins IgG, IgA, IgM, IgD and IgE.

Etiology

Familial clustering of MM has been described. MM presents at an early age in familial cases and there is an increased incidence of other malignancies, both hematological and solid tumors in these families.(37)(38) In a study in Sweeden the MM cases were found to be clustered in families with MM, non Hodgkin lymphoma and chronic lymphocytic leukaemia. There was an autosomal dominant pattern of incidence of familial MM.(39)

Environmental exposure to ionizing radiation, farming pesticides, or possibly petrochemicals also increases the risk of MM. There is an increased incidence of multiple myeloma in persons with rheumatoid arthritis or body mass index of more than 30 kg/ m^2 (40). In majority of the cases there is no obvious etiology.

Pathophysiology

Immunoglobulin molecules contain two linked heavy chains, with one light chain attached to each. Normally, plasma cells produce immunoglobulins to fight infection. However, monoclonal myeloma plasma cells proliferate and overproduce M protein (abnormal IgG, IgM, or IgA, or rarely IgE or IgD). Multiple myeloma cells also produce abnormal light chain proteins (κ or λ), cytokines that stimulate osteoclasts and suppress osteoblasts, and angiogenesis factors that promote new blood vessel formation. Therefore, the multiple myeloma process leads to an excessive M protein level, which causes hyper viscosity; light chain proteins that cause end-organ damage, especially in the kidneys; and invasive bone lesions that cause bone pain, osteoporosis, and hypercalcemia. Bone marrow invasion leads to anemia, and immunologic alterations contribute to recurrent infections.

Clinical features

Presenting clinical features include symptoms of

- Bone disease
- Impaired renal function
- Anemia

- Hypercalcemia
- Recurrent or persistent bacterial infection
- Hyperviscosity

Most patients with MM initially present with unexplained backache or bone pain. Most patients have multiple lytic skeletal lesions involving the long bones, ribs, skull, and pelvis. Pathologic fracture is the presenting symptom in 26 to 34% of patients.(41)(42) Vertebral compression fractures can lead to weakness and paresthesias in the lower extremities. They can also present with features of hypercalcemia such as anorexia, nausea, somnolence, and polydipsia. Weakness and malaise are manifestation of multiple myeloma associated with anemia. Impaired immunoglobulin production and leukopenia lead to recurrent infections, usually from encapsulated organisms. Pneumonia is the most common infection. Weight loss occurs in less than 25% of patients. Unexplained fever is a rare presentation. The incidence of presenting symptoms in multiple myeloma are as given in table 1.(41)(42) Hypercalcaemia, spinal cord compression and renal failure are medical emergencies requiring immediate investigation and treatment. Rare presentations include soft tissue or solitary skeletal plasmacytomas, hyper viscosity-induced arterial infarctions or venous thrombosis, and concomitant amyloidosis with gastrointestinal symptoms, peripheral neuropathy, or cardiomegaly.

Serum protein electrophoresis revealed a localized band in 82% of patients. Urine BJP was found in the urine in 78% of cases. When serum free light chain and immunofixation electrophoresis was used, a monoclonal protein was demonstrable in at least 97% of cases. Nonsecretory myeloma was recognized in 3%, whereas light-chain myeloma was present in 20% of MM.

Conventional radiographs showed an abnormality in 79%. The plasma cell labeling index was ≥ 1% in 34% of patients.(41) M band consisted of IgG isotype in 58-70%, IgA isotype in 24%, light-chain isotype in 11%, IgD isotype in 3%, and biclonal or other isotype in 2-5%.(21)(22)

Investigation and diagnosis

Investigation of a patient with suspected myeloma should include the screening tests, followed by further tests to confirm the diagnosis.(43)

Screening tests:

Full blood count (FBC)

ESR

Urea

Creatinine

Calcium

Albumin

Electrophoresis of serum and concentrated urine

Quantification of non-isotypic immunoglobulins

X-ray of symptomatic areas

Tests to establish diagnosis

Bone marrow aspirate + trephine biopsy with plasma cell phenotyping

Immunofixation of serum and urine

Skeletal survey

Tests to estimate tumor burden and prognosis

Fluorescence in situ hybridisation (FISH) analysis

Quantification of monoclonal protein in serum and urine

Albumin

B_2-microglobulin

Skeletal survey

Tests to assess myeloma-related organ impairment (ROTI)

FBC

Serum urea and creatinine

Creatinine clearance (measured or calculated)

Calcium

Albumin

Tissue biopsy (or fat pad aspirate) for amyloid (if suspected)

Quantification of non-isotypic immunoglobulins

Skeletal survey

Special tests indicated in some patients

Serum free light chain assay in oligo-secretory, light chain only and non-secretory disease

Magnetic resonance imaging (MRI)

Computerised tomography (CT) scan

Quantification of serum M-protein should be performed by densitometry of the monoclonal peak on electrophoresis; immunochemical measurement of total immunoglobulin isotype level can also be used.(43) Quantification of urinary total protein and light chain excretion can be performed directly on a 24-hour urine collection or calculated on a random urine sample in relation to the urine creatinine.(43) The serum free light chain assay is very useful for the

diagnosis and monitoring of light chain only myeloma (44) and in patients with oligo secretory / non-secretory MM.(45) In renal impairment the half life and thus the serum concentration of SFLC can increase tenfold and there is often an increased kappa: lambda ratio.(46) A bone marrow (BM) assessment should be done for confirmation of the diagnosis of myeloma. An adequate trephine biopsy of at least 20 mm in length is recommended in the diagnosis of MM, as it provides a better assessment of the extent of marrow infiltration than aspirate smears.(47)(48)

Diagnostic criteria and differential diagnosis

A diagnosis of myeloma should be made using the International Myeloma Working Group (IMWG) criteria proposed in 2003,(4) which are detailed in Table 2. It is necessary to differentiated between MGUS and asymptomatic myeloma from symptomatic myeloma, since only symptomatic myeloma needs treatment. Difference between an asymptomatic myeloma and symptomatic myeloma is the presence of related organ or tissue impairment. (Table-3)

Prognostication

Age is an independent prognostic factor in Multiple myeloma and, importantly, provides a major criterion by which patients can be considered eligible to tolerate high-dose therapy (HDT) with autologous hematopoietic stem cell transplantation (ASCT).(49) In a study by the International Myeloma working group of 10579 cases, age less than 50 years had an overall survival advantage both after conventional chemotherapy alone and after HDT with stem cell support. (49)

Durie and Salmon staging system (DSS)(50) and International staging system (ISS)(22) have been used for the prognostication of the disease. DSS is based on the assessment of tumor burden. ISS is based on two easily available laboratory parameters (Serum albumin and β2microglobulin). ISS is more widely used because of the ease of risk assessment and its prognostic significance.

Cytogenetic abnormalities which confer an adverse prognosis are t (4;14) and t(14;16) or deletion of chromosome 17, del(17p), by fluorescence in situ hybridization and monosomy or del(13q) or hypodiploidy by metaphase cytogenetics. These cytogenetic abnormalities are present at diagnosis in 25% of patients.(51) Updated Multiple myeloma mSMART consensus guidelines have classified newly diagnosed MM patients into three risk groups. High risk group is defined by the presence of del 17p, t (14; 16), t (14; 20) and high risk signature in the gene expression profiling. Intermediate risk group is defined by the presence of t (4; 14) by FISH, del 13 or hypodiploidy by metaphase cytogenetics or PCLI >3%. Patients with t (4; 14) is considered to have high risk if associated with high β2microglobulin (≥4) and anaemia (≤10 g/dl). Standard risk is defined by all other abnormalities including hyperdiploidy, t(11;14) and t(6;14).(52)

Treatment

The treatment of MM has much evolved from rhubarb pill, infusion of orange peel, phlebotomy and application of leeches in 1840s.(26) Urethane was the first alkylating agent used in the treatment of MM by Alwall in 1947.(53) Subsequently Sarcolysin (Melphalan: L-Phenylalanine mustard) was used by Blokhin et al in 1953.(54) Mass et.al., demonstrated the efficacy of single agent Prednisolone in the treatment of MM in a placebo controlled trial, although there was no survival benefit compared to placebo.(55) Alternate day dosing of Prednisolone was shown to

have efficacy with reduced toxicity.(56) Various combinational chemotherapies were tried in an attempt to treat MM. The classical regimen of Melphalan-Prednisolone(MP) was reported by Alexanian et al, in a randomized trial of 183 patients of MM, in which MP was shown to have a 6 months longer survival compared with single agent Melphalan.(5) Standard induction therapies prior to the advent of novel agents included VAD (vincristine, doxorubicin, dexamethasone), DVD (vincristine, liposomal doxorubicin and dexamethasone) and high-dose dexamethasone with response rates between 40–61%.(57)(58)(59)(60) The CR rates with these regimens are typically low in the range of 3% to 13%. Meta-analysis of individual data of 6633 persons from 27 randomized trials showed a significantly higher response rates with combination chemotherapy than with MP (60.0% v 53.2%; $P < .00001$). However there were no significant differences in the response duration or overall survival.(61) Hence MP remained as the mainstay of MM therapy, until the advent of autologous stem cell transplantation.

The concept of high dose therapy (HDT) evolved in the early 1980s. The first report of HDT using Melphalan 100 to 140 mg/m2 was reported in 1983 by McElwain and Powles (62), the effectiveness of such an approach was confirmed in a subsequent larger study of 63 patients.(63) Autologous stem cell support to overcome the prolonged duration of neutropenia of HDT was proposed by Barlogie et al(6). The Intergroupe Francophone du Mye´lome (IFM) group conducted a randomized trial showing the superiority of HDT with autologous stem cell support compared with conventional chemotherapy (CC).(7) This study showed a better progression free survival (PFS) and overall survival (OS) in the HDT group compared to the conventional chemotherapy group. This result was confirmed in the Medical Research Council VII study involving 400 patients.(8) These two studies established HDT with stem cell support as the standard of care for patients with Multiple myeloma younger than 65 years of age. However

other randomized trials did not show a better OS in the HDT arm compared to the CC arm.(64)(65)(66) Systematic review and meta-analysis of randomized trials showed that ASCT had an impact on the PFS, but not on the OS.(67) The reason for the non significant difference in the OS could be attributable to the availability of better salvage regimens and ASCT after relapse.

In the IFM 90 trial the impact of achieving CR or at least very good partial remission (VGPR) on the OS was shown. Patients who achieved a CR or VGPR had a longer OS than patients who achieved only partial remission (PR). The influence of the depth of response pre and post HDT/ASCT on both EFS and OS was also demonstrated in a study by Lahuretta JJ et.al.(68) The association between complete response after HDT/ASCT and better OS and PFS was shown in a meta-analysis of 21 trial involving 4990 patients.(69)

The ASCT trials used either Melphalan or Total Body Irradiation (TBI) in addition to Melphalan. In an IFM trial Melphalan 200mg/m^2 was compared with Melphalan 140mg/m^2 + 8 Gy of TBI and showed that the event free survival was similar in both groups and the OS was better in the Melphalan 200mg/m^2 group.(70) This established Melphalan 200mg/m^2 as the standard conditioning regimen. Further intensification of therapy was tried using double ASCT. The IFM 94 trial was conducted with the objective of identifying the group of patients, who will benefit from double ASCT.(71) The response to first ASCT, was the only parameter that predicted the benefit of double ASCT. Patients with less than VGPR after the first ASCT had a longer OS in the double-ASCT arm, whereas patients achieving CR or VGPR after the first ASCT had similar OS with or without the second ASCT.

Over the last decade, the survival of patients with newly diagnosed MM, particularly those younger than 60 years, has significantly improved.(9) The widespread use of ASCT and the introduction into clinical practice of the novel agents immunomodulatory derivatives (IMiDs), thalidomide and lenalidomide and the proteasome inhibitor bortezomib have significantly contributed to major advances in the therapy of and its prognosis.(72)(23)

Thalidomide (a-Naphthalimido-glutarimide) is a synthetic derivative of glutamic acid, which was infamous for causing birth defects when used as an antiemetic in pregnancy in the late 1950s and early 1960s. Despite its withdrawal from most markets at this point, it was serendipitously found to be effective in the treatment of erythema nodosum leprosum. Thalidomide has unique immunomodulatory, anti-inflammatory and antiangiogenic properties. The main mechanisms proposed to explain its antimyeloma activity are (73) (74)

(i) immunomodulatory effects on cytokine production and T-cell activation;

(ii) inhibition of cell adhesion;

(iii)antiangiogenic effects; and

(iv)direct inhibition of tumor growth and survival

(v) NF-kappa B suppression

Thalidomide was first used in the treatment of relapsed MM in 1999.(75) A systematic review of phase II trials using single agent Thalidomide in relapsed or refractory MM involving 1674 patients showed an overall response of 29.4% and a median OS of 14 months.(10) The dose of Thalidomide used ranged between 50 mg/day to 800 mg/day.(10) In a prospective randomized study, 400 patients with relapsed or refractory MM were treated with thalidomide at a dose of

100 mg/day or 400 mg/day, and the two dosage had no significant difference in 1-year OS (73% vs. 69%, respectively).(76)

Preclinical studies had shown that both thalidomide and lenalidomide (IMiDs) potentiate the activity of dexamethasone, providing the rational for the combination therapy of IMiDs with Dexamethasone.(77) Subsequently trials established the superiority of Thalidomide-Dexamethasone combination therapy in relapsed/refractory MM compared to single agent Thalidomide(Response rate 50% vs. 30%).(78) These studies provided the rationale for subsequent phase 2 and 3 trials investigating the role of this regimen in patients with newly diagnosed MM.

In 2005, a retrospective case-matched study by Cavo et.al., demonstrated the superior rate and depth of response affected by TD compared with VAD as induction therapy in preparation for ASCT,(79) This finding was confirmed in a subsequent phase 3 study.(80) Phase II trials of TD in newly diagnosed MM showed a response of 65% to 70%, similar to VAD chemotherapy.(81)(82)(83) Moreover TD has the convenience of oral administration and no cardiotoxicity or alopecia seen with VAD. Based on the results of a randomized study showing a higher response rate with TD compared with high-dose dexamethasone(11), the United States Food and Drug Administration granted accelerated approval for TD in patients with newly diagnosed MM. As a result, over the past years, TD has emerged as one of the most commonly used induction regimens in the United States and European countries (European Union).

In the ECOG E1A00 trial, TD demonstrated superior response rates compared to dexamethasone (63% vs. 41%, $P = 0{\cdot}0017$) following 4 months of induction therapy.(11) In the MM003 trial, TD significantly prolonged time to progression (TTP) compared with dexamethasone alone

(median 22·6 months vs. 6·5 months, $P < 0·001$); however, no conclusion regarding survival could be drawn from this study as it was not powered to compare survival.(84) In a French trial comparing TD with VAD, the improvement in ≥VGPR rate achieved with TD *versus* VAD post-induction did not translate to an improvement in post-transplant ≥VGPR for TD over VAD; There was no survival benefit.(80)

In all studies, TD and TAD were superior to VAD in terms of overall response and VGPR rates (Table 3). However, the thalidomide-based regimens did not increase the CR rate prior to ASCT, which remained at a very low < 10%. Post-ASCT results were analyzed in two trials: Although VGPR rates with TD and VAD were similar; VGPR rates were superior with TAD as compared with VAD (Table 3). The drawback of thalidomide therapy includes a high incidence of deep vein thrombosis, up to 26% and peripheral neuropathy. (83) The role of other novel agents in the therapy of MM is beyond the scope of this study.

Maintenance therapy

Maintenance therapy is given after the patient achieves a response to an initial therapy of myeloma with the goal of extending the PFS and OS, while maintaining a good quality of life.

Several randomized studies shown a PFS benefit with thalidomide as single agent or combined with prednisone as maintenance therapy after ASCT.(85)(86)(87)(88)(Table 4). In 2 of these studies, OS was extended in the thalidomide arm.(87)(88) This advantage was lost when thalidomide was also given as part of induction therapy before ASCT.(85)(86) There are two studies of Thalidomide maintenance post conventional chemotherapy demonstrating better PFS compared to Interferon or interferon + Dexamethasone. (12)(13) However the OS benefit was there in only one of the studies.(13) The major limitation that precludes a widespread use of

thalidomide maintenance is the toxicity related to long-term administration of this agent, primarily peripheral neuropathy (PN). In several studies, thalidomide-induced PN led to discontinuation rates in the 60% range. (85)

Concluding remarks

The treatment of Multiple myeloma has evolved over time. With the availability of autologous stem cell transplantation and the advent of novel agents, the rate of complete response has increased and the progression free survival and overall survival have improved. There is a role for maintenance therapy in the management of multiple myeloma.

Aims and Objectives

- To analyze the response rate, progression free survival and overall survival of newly diagnosed multiple myeloma cases treated with Thalidomide-Dexamethasone as induction therapy.
- To analyze impact of ASCT and Thalidomide maintenance in prolonging the progression free survival and overall survival.

Patients and methods

This study protocol was approved by our Institutional Review Board (IRB).

Duration of the study: March 2004 to December 2011.

Settings of the study: Department of Clinical Haematology.

Diagnostic criteria: According to the International Myeloma Working Group (IMWG) criteria for diagnosis of Multiple myeloma, 2003. (Table-2)

PATIENTS

Inclusion criteria:

- All patients with newly diagnosed multiple myeloma seen in the Department of Hematology between March 2004 to September 2011, who were initiated on Thalidomide-Dexamethasone as first line therapy.

Exclusion criteria:

- Patients with multiple myeloma treated with regimens other than Thalidomide-Dexamethasone as first line therapy.
- Patients diagnosed and initiated on Thalidomide-Dexamethasone in other hospitals before coming to CMCH for further management.

METHODS

Data collection

After approval by the IRB, the patient data base at our institution were reviewed to identify all patients with newly diagnosed multiple myeloma who were initiated on Thalidomide-Dexamethasone as first line therapy at our institute from March 2004 to September 2011. Medical information regarding the clinical/laboratory details at diagnosis, post treatment response and adverse events were obtained from the hospital records (laboratory reports/ physician documentation in hospital charts/hospital discharge summaries). Patients who after initiating therapy with TD did not have at least one response assessment were categorised as '**lost to follow up'** and were excluded from the analysis for progression free and overall survival.

Treatment

All patients were initiated on Thalidomide at a dose of 50mg to 100mg OD and the dose was increased gradually to 400mg once daily if tolerated. Dexamethasone 20mg - 40mg OD was given on D1-4, 9-12 and 17-21 during the first month, then on D1-4 from subsequent cycles.

ASCT was done in patients affording transplant after they achieve a response to therapy.

Maintenance thalidomide was initiated as per physician discretion in patients who achieve a response to initial therapy.

Response criteria

The response will be assessed as per the International Myeloma Working Group uniform response criteria.(89) (Tables – 6 and 7)

CRu (Complete response unconfirmed)

Bone marrow is not done as a routine at the time of response assessment at our institution, except prior to ASCT. Hence we defined this category of response "CRu" as absence of M protein, normal serum free light chain or immunofixation electrophoresis without bone marrow analysis.

Data analysis

Statistical analyses were performed with SPSS (windows 11.01 version, SPSS inc, Chicago), for all variables. Descriptive statistics was calculated for all variables. The χ^2 test/ Fishers exact test or *t*-test / Mann Whitney U test was used as appropriate to compare the differences between groups for response to therapy.

Patients who were having PD, but alive at the time of last follow up and not followed up for more than six months or were sent on palliative intent as per discharge summary/OP chart were considered dead for the statistical analysis

Overall survival (OS) was defined as time from diagnosis to death due to any cause. Progression free survival (PFS) was defined as time from initiation of TD to disease progression or death resulting from any cause. The OS and EFS was estimated using Kaplan-Meier method. For all tests, a two-sided *p*-value of 0.05 or less was considered statistically significant.

RESULTS

A total of 242 patients with newly diagnosed MM were initiated on Thalidomide-Dexamethasone therapy during the study period. Of the 242 cases, 17 cases did not have even a single response assessment after the initiation of therapy with Thalidomide-Dexamethasone. These patients were only included for the analysis of baseline characteristics and excluded from analysis of progression free and overall survival. Hence a total of 225 patients were available for response and survival analysis.

Certain data are available on all patients, while other data are available only on a portion of the patients. For each result category, the numbers of patients involved are mentioned.

Demographic data (table-8)

The median age of the 242 patients was 54 years (range 21-80). The proportion of cases younger than 65 years and 50 years was 90.4% and 34.7% respectively. Males were predominantly represented in the 242 patients. 172(71.1%) were males and 70(28.9%) were females. The male female ratio was 2.45:1

Clinical presentation (Table-9)

Anaemia and back pain was the most common presenting feature in 59.1% and 57.4% respectively. Renal failure was documented in 21.1%. Vertebral wedge compression fractures were present in 47.9%. Pathological fractures involving the long bones were the presenting feature in 13 cases, with the humerus and femur being the most commonly affected bones. Paraparesis due to extradural cord compression was seen at the time of diagnosis in 17 cases

(7%). Unexplained weight loss and pyrexia of unknown origin were present at diagnosis in 6.6% and 4.9% of cases respectively. Seven patients presented with infection, urinary tract infection in 5, pneumonia and diarrhea in one patient each. Peripheral neuropathy, DVT, lymphadenopathy, proptosis and polyarthritis were some of the rarer presentations. Hypertension (11.9%) and diabetes mellitus (9%) was the most common comorbidities seen at diagnosis. Other comorbidities included hypothyroidism (3 patients), bronchial asthma, coronary artery disease and benign prostatic hypertrophy in 2 patients each, ankylosing spondylitis, previous renal cell carcinoma, previous cerebrovascular accident and Parkinson disease in one patient each.

Anaemia, Thrombocytopenia and Leukopenia (Table-10)

Anaemia, thrombocytopenia and leukopenia were present in 59.1% of patients, 6.6% and 3.3% respectively. Serum creatinine >2mg / dl and a corrected serum calcium >10.5 mg/dl was documented in 21.1% and 19.8% respectively.

Hypoalbuminemia and β2 microglobulin <3.5 mg/l was present in 46.7% and 35.7% respectively. Elevated uric acid and serum LDH was documented in 55.8% and 20.9% of patients. Urine BJP was positive in 63.6% of patients and the 24 hour urine protein greater than 200mg / day was documented in 75.4%.

Heavy chain myeloma was predominant type with IgG, IgA and IgM constituting 55.7%, 13.2% and 1.6% respectively. The type of heavy chain was not available in 16 cases. Light chain myeloma and non-secretory disease constituted 18.2% and 1.2% respectively. Biclonal M band was present in 8 cases (3.3%). Associated amyloidosis was present in 4 patients.

Bone involvement was present in a total of 200 patients (82.6%). Lytic lesion were seen in 134 (55.3%) of cases. Long bone pathological fractures were seen in 5.3%. Plasmacytoma was

present in 57% of cases, out of which extramedullary plasmacytoma was present in 6 cases. Sclerotic lesions were present in 2 cases. Osteopenia was present in 11.9% of cases.(Table-11)

Progression of MGUS and solitary plasmacytoma to symptomatic multiple myeloma occurred in 1 and 5 patients respectively. The time to progress to MM from the diagnosis of MGUS was 52 months and from the diagnosis of solitary plasmacytoma was between 44-65 months with a mean of 52 months. (Table-12)

The proportion of patients according to the ISS stage was 25.4%, 32.5% and 42.1% for ISS I, II and III respectively. The proportion of patients according to the DSS was 12.8%, 35.5% and 51.7% respectively for DSS I, II and III respectively. (Table-13)

Treatment with Thalidomide-Dexamethasone (TD) (Table-14, 15 & 16)

All the 242 patients were initiated on TD. Seventeen cases were lost to follow up. Among the remaining 225 patients, the median number of cycles administered was 7 (range: 1 to 27). TD was administered for >1yr in 40 cases. The median dose of Thalidomide was 200mg OD (range: 50 – 400mg OD). The median dexamethasone dose was 40mg OD (range: 8 -40 mg OD). DVT prophylaxis was given to 219 cases, 217 receiving aspirin. One patient continued clopidogrel, which was started for cerebrovascular event in the past. One patient with a lower limb DVT at presentation was on anticoagulation with Sintrom prior to starting TD. No prophylaxis was given in 23 patients. Bisphosphonates were given to 173 patients (71.5%).

Response to TD (Table-17)

Of the 225 patients available for analysis, 181(80.5%) achieved a response and 44 were non responders. CR, CRu, VGPR and PR rates were 4.5%, 4.5%, 31.1%, and 40.4% respectively. The median time to response was 3 months (range: 1month to 13 months).

The response according to ISS and DSS (Table-18)

Response and survival did not vary according to ISS and DSS categories. The overall survival of the ISS I, II and III were 90.1%, 79.6%, and 72.7% at a median follow up of 22.5 months, 26 months and 28 months respectively (p=0.055). The overall survival of the DSS I, II and III were 86.6%, 79.5%, and 78.5% at a median follow up of 20 months, 25 months and 25.5 months respectively.

After achieving an initial response to TD 153 developed progressive disease. The median time to progression was 11 months (range 1-86 months).

Subsequent course

Among the responders, 13 patients **(ASCT group)** underwent upfront ASCT post induction therapy, 49 patients **(Maintenance group)** received Thalidomide maintenance (one patient received Lenalidomide maintenance) therapy, while 119 patients **(No treatment group)** did not receive any further therapy.

Maintenance group (Figure-4)

Maintenance was initiated in 49 of 181 patients achieving a response to TD. Thalidomide at a median dose of 100mg OD (range: 50mg to 200mg OD) was given to 48 patients. One patient received Lenalidomide maintenance. Duration of maintenance therapy ranged from 2-69 months with a median duration of 14 months. The median dose of Thalidomide during maintenance was 100mg OD.

Of the 49 patients who were on maintenance therapy 21 remain in remission at a median follow up of 32 months and 28 had progressive disease with a median time to progression of 17.5

months. All 28 patients with progressive disease received treatment with various second line regimens and one patient underwent ASCT (follow up of 15 months), while 7 patients expired (median follow up of 37 months) with progressive disease and 20 patients were alive (median follow up of 50 months).

No treatment group (Figure-5)

Of the 119 patients who neither received maintenance nor ASCT, 40 remained in continuous response (median follow up of 8 months), while 79 had progressive disease. The median time to progression was 11 months. Among the 79 patients who relapsed, 4 did not receive any further therapy and the rest were treated with various second line therapies. Nine of these patients underwent a successful ASCT out of which 7 are alive, in continued response (median follow up of 35 months) and 2 are dead with progressive disease. Among the 79 patients who relapsed, 17 had refractory disease and expired due to progressive disease (median follow up of 17 months) and 49 are alive after subsequent therapy.

Non – responders (Figure-6)

Of the 44 patients who were non responders (Minimal response-14, No response-23, Progressive disease-7), 5 patients did not undergo any further therapy while 39 were treated with salvage therapy. Six patients underwent ASCT after achieving a response and 5 patients of this group are alive (median follow up of 37 months). Thirteen expired due to progressive disease (median follow up of 12 months) and 20 patients were alive at last follow up after salvage therapy (median follow up of 28 months).

ASCT (Table-23)

A total of 29 patients underwent ASCT, 13 patients post TD induction and 16 patients post salvage therapy. The median age of the patients undergoing ASCT was 50 yrs (range: 29 to 59 yrs). The median from diagnosis to ASCT was 12 months (range: 4 -32 months). The number of chemotherapy regimes received prior to the transplant was one in 13 patients, 2 in 11 patients and three in 5 patients. Pre transplant CR/CRu was present in 9 patients, VGPR in 11 patients and PR in 9 patients. The median dose of Melphalan was 200mg/m^2. The median CD34 cell dose was 3.8 $X10^6$ cells/ Kg (range: 1.15 to 17 $X10^6$ cells/ Kg). Mucositis was occurred in all patients with grade III/IV in 23 patients. The median time to ANC >500/cu.mm, >1000/cu.mm and platelet >20000/cu.mm was 11 days, 12 days and 12 days respectively. The median duration of post ASCT follow up was 15 months (range: 1-74 months). Post transplant CR/CRu was achieved in 15 patients, VGPR in 8 patients, PR in 5 patients and one patient had progressive disease. Eleven patients had progressive disease post transplant and the median time to progress post transplant was 13 months (range: 2-44 months).

Among the 13 patients who underwent upfront ASCT, all but one achieved ≥VGPR and one patients achieved PR. Except for the 2 patients who relapsed post ASCT, the 11 of the 13 patients receiving upfront ASCT were alive in continuous remission, with a median follow up of 72 months. (Figure-3)

An additional 16 patients underwent ASCT after achieving remission with salvage therapy and 11 achieved ≥ VGPR and 4 PR while one patient had PD. Among these 9 had progression of disease post transplant with median time to progression of 13 months (range: 4-44 months) and received further chemotherapy. Among the 16 patients, 13 are alive and 3 patients are dead with progressive disease at a median follow up of 33 months.

Post ASCT maintenance was initiated in 14 patients, 11 received Thalidomide and 3 received Lenalidomide. The median dose of thalidomide maintenance was 100mg OD (range: 100 – 200mg OD). The median duration of maintenance therapy was 10 months (range: 2-30 months). Seven patients who had maintenance post ASCT had PD, with a median TTP of 13 months (range: 6-44 months). Four patients without maintenance post ASCT had PD, with a median TTP of 12.5 months (range: 4-16 months).

Adverse effect (Table-22 and 24)

Peripheral neuropathy due to thalidomide was noted in 21.3% of patients. They were mainly sensory symptoms with no documented motor deficits. However nerve conduction studies were not done to document neuropathy. Thalidomide had to be stopped due to neuropathy in 8 patients at the following time periods: 3mo(2 patients), 9mo(1 patient), 15mo(1 patient), 18mo(2 patients), 19 mo (1 patient) and 32 mo(1 patient). In an additional 11 patients, the dose of thalidomide had to be reduced. Constipation was the most commonly encountered adverse effect, occurring in about 22.2%. However it usually occurred during the initiation of therapy and responded to laxatives and settled over time on continuation of thalidomide. Hyperglycemia was seen in about 12.1% related to Dexamethasone. Somnolence and rash were noted in 5 patients each. The rash subsided on discontinuation of Thalidomide. However 3 of the patients continued thalidomide uneventfully. DVT of the lower limb was present in one patient at the time of diagnosis, who was initiated on TD after adequate anticoagulation with Sintrom. He did not develop any recurrent thrombo-embolic manifestations. Six patients (2.6%) developed documented venous thrombosis while on Thalidomide. Except for one of these patients all were on aspirin prophylaxis. One patient had associated polycythemia vera with JAK 2 mutation. One patient had chronic pulmonary thromboembolism and one had cortical vein thrombosis. Other

rare adverse events noted were grade IV myopathy, depression, cushing syndrome, syncope, seizures, pancreatitis and neutropenia in one patient each.

Overall survival (OS) and Progression free survival (PFS)

Two hundred and twenty five patients could be analyzed for PFS and OS. The median follow up was 24 months (range: 1-96 months). There were a total of 45 deaths, all due to progressive disease and none were related to toxicity of therapy. Among the 45 deaths 13 were documented in our institution. The remaining cases were considered dead as per criteria defined in the methods.

The median PFS (Figure-7) was 14 months (95% CI: 21.3 to 29.6 months) with the PFS at 24 months and 36 months were 38.3% and 26.3% respectively. The median for OS (Figure-8) has not been reached and the mean OS was 70 months (95% CI: 64 to 77 months). The OS at 24 months and 36 months were 84.5% and 76.9% respectively.

Median PFS for patients undergoing upfront ASCT (Figure-9) has not been reached and the mean PFS is 69.1 months (95% CI: 47.8 to 90.3 months). The PFS at 24 and 36 months were 100% and 83.3% respectively. Median OS (Figure-10) of patients undergoing upfront ASCT group has not been reached and the mean OS was 70 months (95% CI: 56 to 83 months). The OS at 24 and 36 months were 95.4% and 82.7% respectively.

In patients receiving maintenance after TD, the median PFS (Figure-9) was 38 months (95% CI-23.4 to 52.5 months) with the PFS at 24 months and 36 months were 66.6% and 55.1% respectively. The median OS (Figure-10) in the maintenance group has not reached and the mean OS was 81 months (95% CI-71 to 91 months) and the OS at 24 months and 36 months were 95.6% and 92.4% respectively.

In patients who did not receive either ASCT or maintenance post TD, the median PFS (Figure-9) was 14 months (95% CI: 17 to 23.6 months) with the 24 month and 36 month PFS being 31% and 14.7% respectively. The median OS (Figure-10) has not been reached in the no ASCT/ no maintenance group with mean OS of 61 months (95% CI: 52 to 70 months). The OS at 24 and 36 months in this group was 82.9% and 75.2% respectively.

The ASCT group had a statistically significant PFS benefit over the Maintenance group, which had a statistically significant better PFS than the No ASCT / No maintenance group (p=0.000). However there was no significant difference in the overall survival among the three groups (p=0.1064).

Discussion

The median age of the 242 patients was 54 years (range 21-80). The proportion of patients younger than 65 years was 90.4% and this is far higher than what is reported in the western population. The proportion of cases younger than 65 years was 90.4%. The median age at diagnosis reported in western literature is between 60yrs to 70 yrs.(19),(22) The median age of the two phase III trials of TD upfront treatment were 64 and 65 years, much older than in this study.(11)(84)

Males were predominantly represented in the 242 patients. 172(71.1%) were males and 70(28.9%) were females. The male female ratio was 2.45:1. In the published western literature males are predominant with 55%.(2) Anaemia, thrombocytopenia and leukopenia were present in 59.1% of patients, 6.6% and 3.3% respectively. A review of 1027 patients from Mayo clinic reported anaemia in 72% of patients at diagnosis.(41)(42). Serum creatinine >2mg / dl and a corrected serum calcium >10.5 mg/dl was documented in 21.1% and 19.8%, which is similar to that reported from the Mayo clinic. (41) Similar to the present study the bone involvement were reported in 80% of the cases, which includes lytic lesions, pathological fractures and osteopenia.(41) However the pathological fractures were less in the present study compared to that in the literature of 13%(41). The type of myeloma (Heavy chain, light chain and non secretory) was similar in the present study compared to the mayo clinic study. (41)

The proportion of patients according to the DSS staging are similar to a report published in 2007.(90)

Progression of MGUS and solitary plasmacytoma to symptomatic multiple myeloma occurred in 1 and 5 patients respectively. MGUS and solitary Plasmacytomas are known to progress to overt MM.(15),(16) A recent publication showed that all cases of overt MM were preceded by MGUS.(3)

The reported adverse effects of TD therapy in the literature are constipation 33% to 72%, peripheral neuropathy 3.4% to 72%, rash 0% to 61%, thrombosis 4% to 18.8% and infection in 7.3%, which are similar to that in the present study. (81) (82) (79) (80) (71) (83) (84) (91) The incidence of thrombotic complications in this study is lower (2.6%) compared to that reported in the western countries. This may be related to the use of aspirin prophylaxis in majority of patients (89.6%) in the current study. Palumbo et.al, has reported a reduction in the incidence of thrombosis in patients treated with Melphalan, Thalidomide and Dexamethasone (MPT) with enoxaparin prophylaxis to 3%.(92)

In the largest phase III randomized trial of TD treatment in newly diagnosed MM, the median number of cycles was 6.9 and median dose was 200mg OD, which is similar to the present study. (72)

Of the 225 patients available for analysis, 181(80.4%) achieved a response while 44 were non responders. CR, Cru, VGPR and PR were achieved in 4.5%, 4.5%, 31.1%, and 40.4% respectively. The time to response ranged from 1 month to 13 months with a median time to response of 3 months. The various phase II and Phase III trials showed an overall response of 63% to 76%, VGPR or greater response according to published literature ranged between 19% to 43.8% and CR was reported in 2% to 10%, which is similar to the present study. (Table 24)

The median time to progression was 11 months (range 1-86 months). The median time to progress in a phase III randomized trial of TD treatment in newly diagnosed MM without ASCT was 22.6 months. (72)

Age, sex, anaemia, renal failure, hypercalcemia, bone involvement, presence of plasmacytoma, hypoalbuminemia and β2 microglobulin >3.5 mg/l, type of myeloma, i.e., heavy chain, light chain, biclonal or nonsecretory myeloma, bone marrow plasma cell percentage below or above 50%, ISS and DSS staging, urine BJP and 24 hour urine protein did not significantly affect the response, PFS and OS to Thalidomide -Dexamethasone therapy. Age is an important prognostic marker with younger age group having a better response and overall survival compared to older age group. In this study 34.7% of patients were younger than 50 years. Survival advantage in age <50yrs compared to age >50 yrs, both after conventional therapy and after ASCT has been reported based on study of 10549 patients (median, 5.2 years vs. 3.7 years; $P < .001$). (49) However in the present study age was not significant for both OS and PFS.

In the group of patients who received maintenance therapy, the median PFS was 38 months (95% CI-23.4 to 52.5 months) and the PFS at 24 months and 36 months were 66.6% and 55.1% respectively. The median OS has not been reached and the mean OS was 81 months (95% CI-71 to 91 months) and the OS at 24 months and 36 months were 95.6% and 92.4% respectively. These findings were statistically significant compared to patients who did not receive maintenance therapy, where the median PFS was 14 months (95% CI: 17 to 23.6 months) and the 24 month and 36 month PFS was 31% and 14.7% respectively. The median OS however has not been reached with a mean OS of 61 months (95% CI: 52 to 70 months). The OS at 24 and 36 months in this group was 82.9% and 75.2% respectively. Offidani et.al., published data on Thalidomide + Dexamethasone maintenance post induction therapy (median age of 72 yrs) and

showed a PFS at 24 months of 63% and OS at 24 months of 83 %.(12) In another study Thalidomide + Interferon maintenance therapy in elderly subjects after induction therapy with either TD or MP by Ludwig, H. et al, the median PFS was 27.7 months and the median OS was 52.6 months.(13) The superior PFS and OS in the present study compared to the published data could be probably due to the younger age of the cases.

The number of chemotherapy regimens received prior to the transplant, pre transplant status, the CD34 cell dose, baseline characteristics at diagnosis and post transplant maintenance therapy did not significantly impact OS or time to progress after autologous transplant. The median duration of post ASCT follow up was 15 months (range: 1-74 months). Post transplant CR/CRu + VGPR has been achieved in 23(79.3%) of the total 29 patients. Data in literature shows a post TD induction and ASCT a >VGPR rate of 44%(11) and 54%. (86)

Post ASCT maintenance was initiated in 11 patients, 11 received Thalidomide and 3 received Lenalidomide. Seven patients of the post ASCT maintenance group had PD, with a median TTP of 13 months (range: 6-44 months). Four patients of the no maintenance post ASCT group had PD, with a median TTP of 12.5 months (range: 4-16 months). Published literature on Thalidomide maintenance post ASCT show PFS and OS advantage in 2 trials(87)(88) and PFS advantage but no OS advantage in one trial.(86)

The response to TD (CR + CRu vs. VGPR vs. PR) was significantly associated with a better PFS (p=0.000), however was not significant for OS (p=0.232). In the IFM 90 trial the impact of achieving CR or at least very good partial remission (VGPR) on the OS was shown. Patients who achieved a CR or VGPR had a longer OS than patients who achieved only partial remission

(PR). The influence of the depth of response pre and post HDT/ASCT on both EFS and OS was also demonstrated in a study by Lahuretta JJ et.al.(68)

The median follow up duration was 24 months (range: 1-96 months). The median PFS was 14 months (95% CI: 21.3 to 29.6 months). The PFS at 24 months and 36 months were 38.3% and 26.3%. The median PFS of the TD arm in a randomized study by Rajkumar et.al., was 14.9 months which is similar to that of the present study.(84)

The median for OS has not been reached and the mean OS was 70 months (95% CI: 64 to 77 months). The OS at 24 months and 36 months were 84.5% and 76.9%. The median OS of patients undergoing ASCT after TAD reported in literature is 73 months. (86) The two Phase III trials with upfront TD has not reported OS.(11) (84) (Table 26)

Summary

- A total of 242 newly diagnosed patients were initiated on TD, out of which 225 were available for analysis. The median follow up was 24 months (range: 1-96 months)
- The median age of the cohort was 54 years which is younger than that reported in the literature.
- A total of 80.5% of patients responded to TD, with a ≥VGPR rate of 40.1% and a CR + CRu rate of 9%.
- ISS and DSS did not have a significant effect on the response or survival.
- PFS in the three groups ASCT, Maintenance, No treatment (No ASCT/ No maintenance were) was 83.3%, 55.1%, and 14.7% at 36 months respectively. (p=0.0000).
- PFS and OS of the entire cohort of patients were 26.3% and 76.9% at 36 months respectively.
- Incidence of neuropathy was 21.3% and thrombosis was 2.6%. Thalidomide had to be discontinued in 8 patients due to peripheral neuropathy and in 3 patients due to rash. Dose reduction of thalidomide was done in 11 patients due to peripheral neuropathy.

Limitations of the study:

1. It is a retrospective study.

2. No randomization of cases to ASCT, maintenance or no ASCT/no maintenance therapy.

3. Cytogenetics study, which is an important prognostic marker, has not been done.

Conclusions

- **Thalidomide – Dexamethasone is an effective first line therapy for multiple myeloma.**
- **Autologous stem cell transplantation and Thalidomide maintenance therapy prolongs progression free survival, however overall survival is not affected.**

Figures and Tables

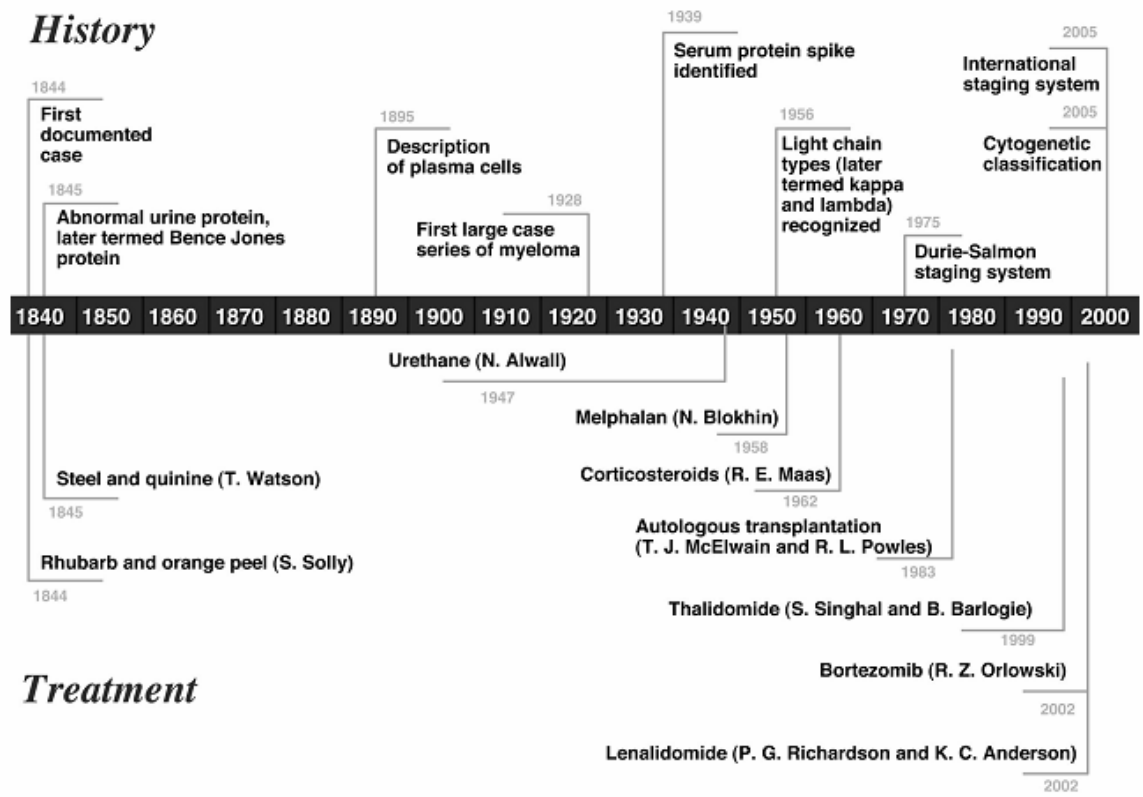

Fig.1: Timeline depicting the history and treatment of Myeloma

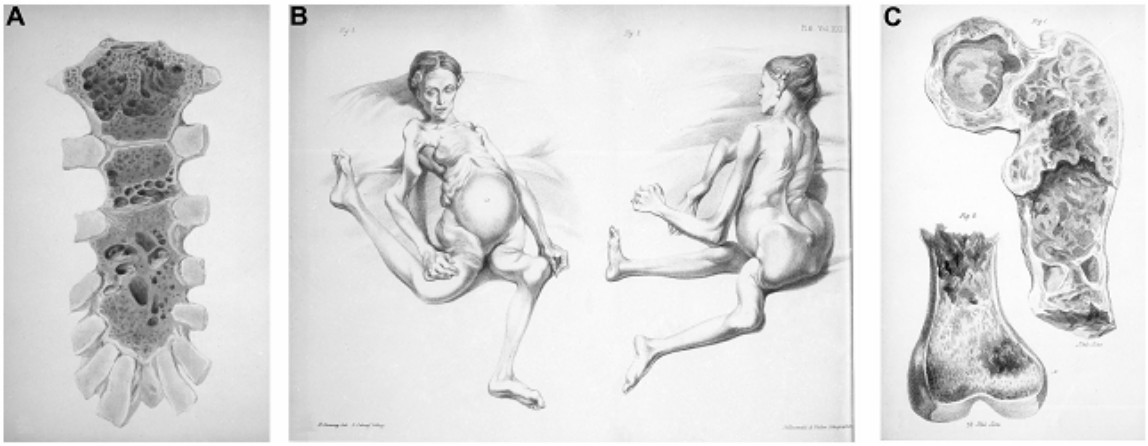

Fig.2: Sarah Newbury, the first reported patient with multiple myeloma. (A) Bone destruction in the sternum. (B) The patient with fractured femurs and right humerus. (C) Bone destruction involving the femur. (25)

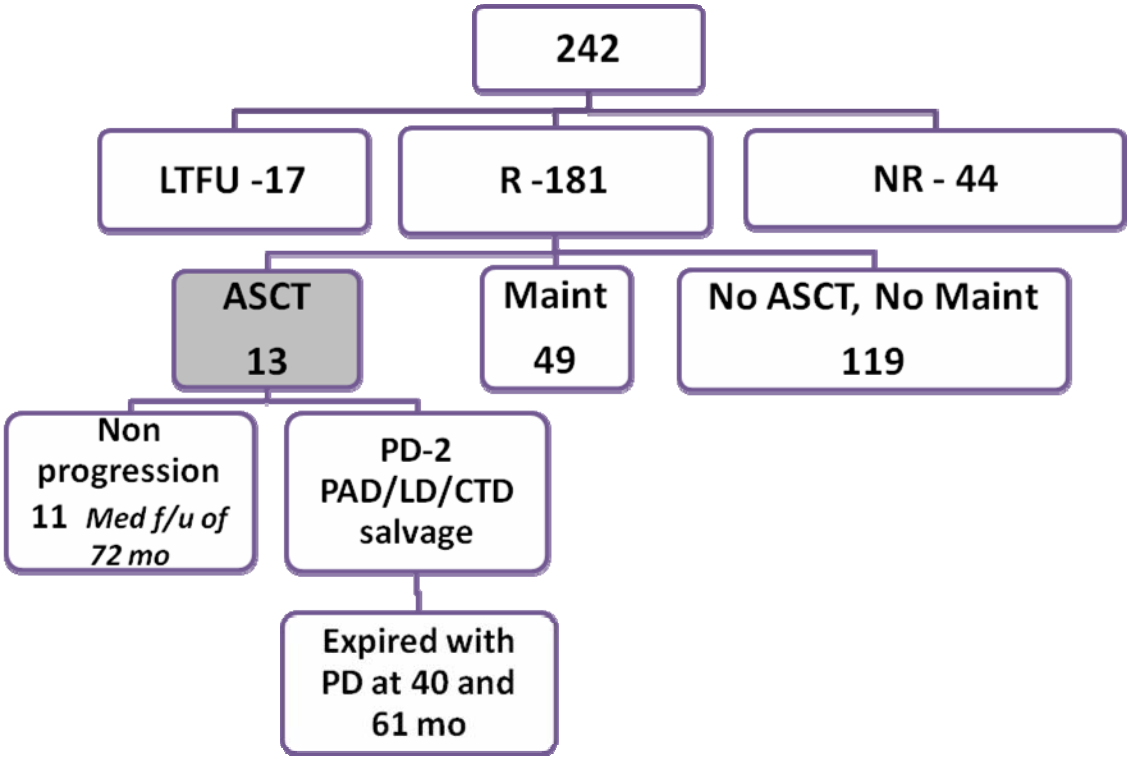

Figure-3: Flow chart depicting the response to Thalidomide – Dexamethasone and subsequent course of patients undergoing upfront ASCT. R-Responder, NR-Non responder, LTFU-Lost to follow up, ASCT – Upfront Autologous stem cell transplantation group, Maint – Thalidomide maintenance group, No treatment group – No Autologous stem cell transplantation and no maintenance group, PD-Progressive disease, mo-months, med f/u- Median follow up, CTD- Cyclophosphamide + Thalidomide + Dexamethasone, LD – Lenalidomide + Dexamethasone, PAD – Bortezomib + Adriamycin + Dexamethasone. CR-Complete remission, CRu-Complete response unconfirmed, VGPR-Very good partial response, PR-Partial response.

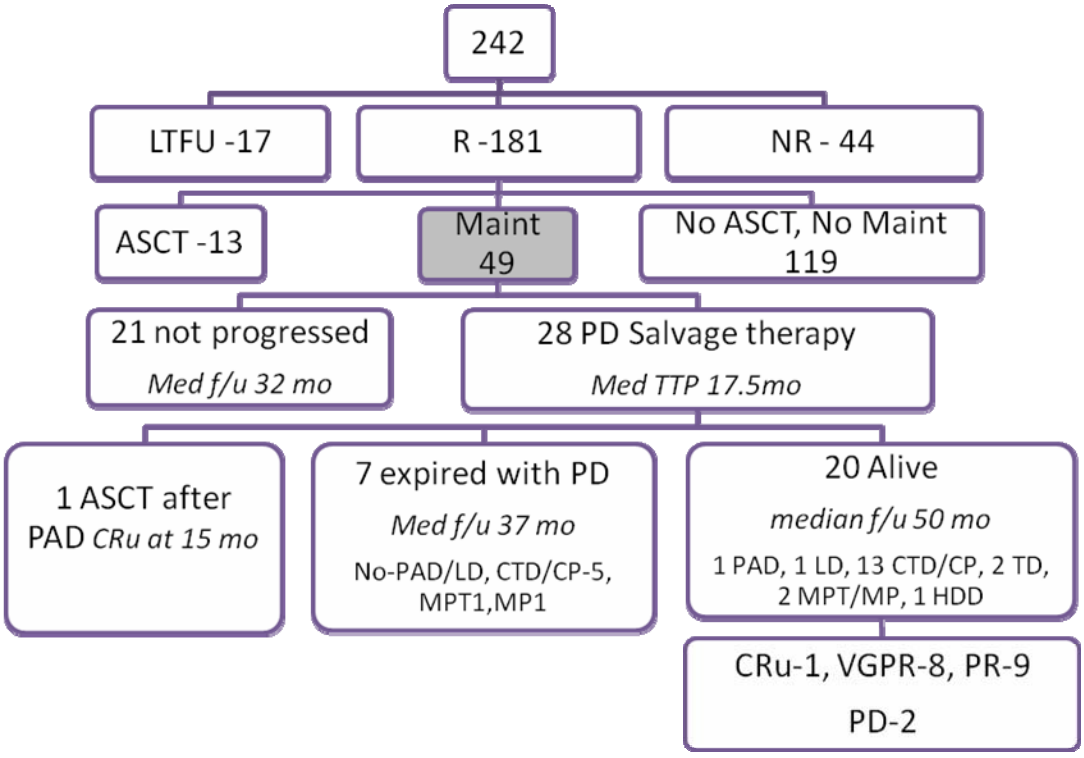

Figure-4: Flow chart depicting the response to Thalidomide – Dexamethasone and subsequent course of patients initiated on thalidomide maintenance. R-Responder, NR-Non responder, LTFU-Lost to follow up, ASCT – Upfront Autologous stem cell transplantation group, Maint – Thalidomide maintenance group, No Treatment group – No Autologous stem cell transplantation and no maintenance group, mo-months, med f/u-Median follow up, PD-Progressive disease, Cyclo-Pred-Cyclophosphamide + Prednisolone, CTD-Cyclophosphamide + Thalidomide + Dexamethasone, MP-Melphalan + Prednisolone, MPT – Melphalan + Prednisolone + Thalidomide, LD – Lenalidomide + Dexamethasone, , PAD – Bortezomib + Adriamycin + Dexamethasone. CR-Complete remission, CRu-Complete response unconfirmed, VGPR-Very good partial response, PR-Partial response.

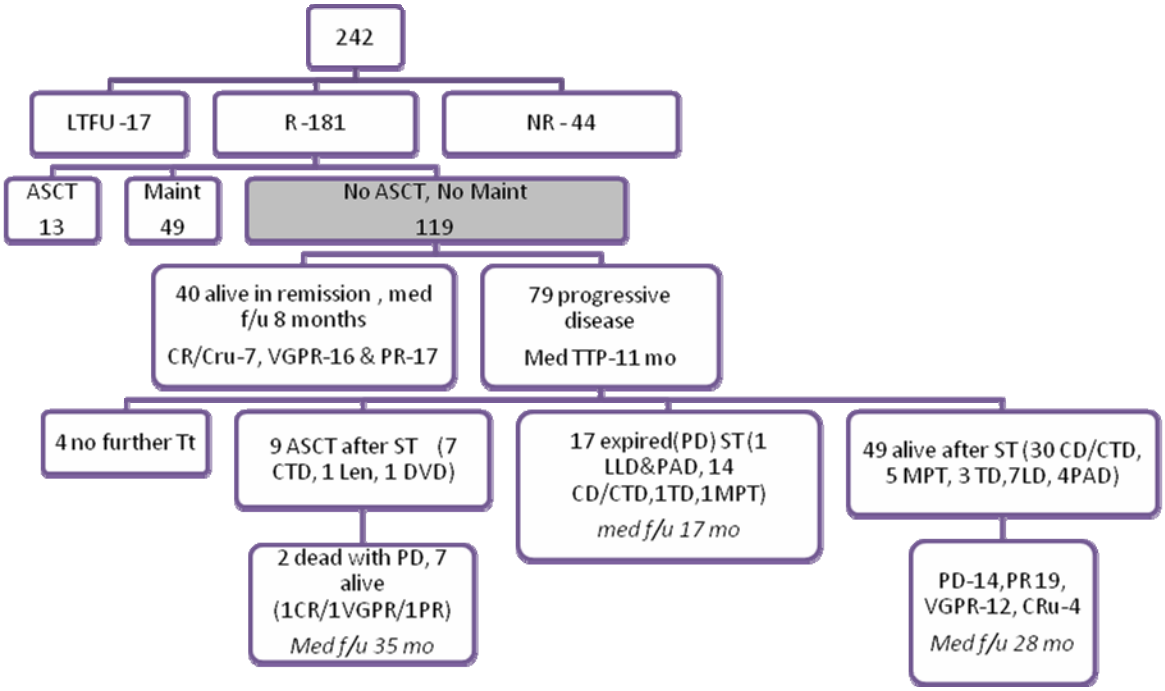

Figure-5: Flow chart depicting the response to Thalidomide – Dexamethasone and subsequent course of patients not initiated on thalidomide maintenance or ASCT after initial response to TD. R-Responder, NR-Non responder, LTFU-Lost to follow up, ASCT – Upfront Autologous stem cell transplantation group, Maint – Thalidomide maintenance group, No treatment group – No Autologous stem cell transplantation and no maintenance group, PD-Progressive disease, mo-months, med f/u-Median follow up, PD-Progressive disease, Cyclo-Dex- Cyclophosphamide + Dexamethasone, Cyclo-Pred-Cyclophosphamide + Prednisolone, CTD- Cyclophosphamide + Thalidomide + Dexamethasone, MP-Melphalan + Prednisolone, MPT – Melphalan + Prednisolone + Thalidomide, LD – Lenalidomide + Dexamethasone, LLD – Lenalidomide + Pegylated Liposomal Doxorubicin + Dexamethasone, PAD – Bortezomib + Adriamycin + Dexamethasone,ST-Salvage therapy, Tt-Treatment, CR-Complete remission, CRu-Complete response unconfirmed, VGPR-Very good partial response, PR-Partial response

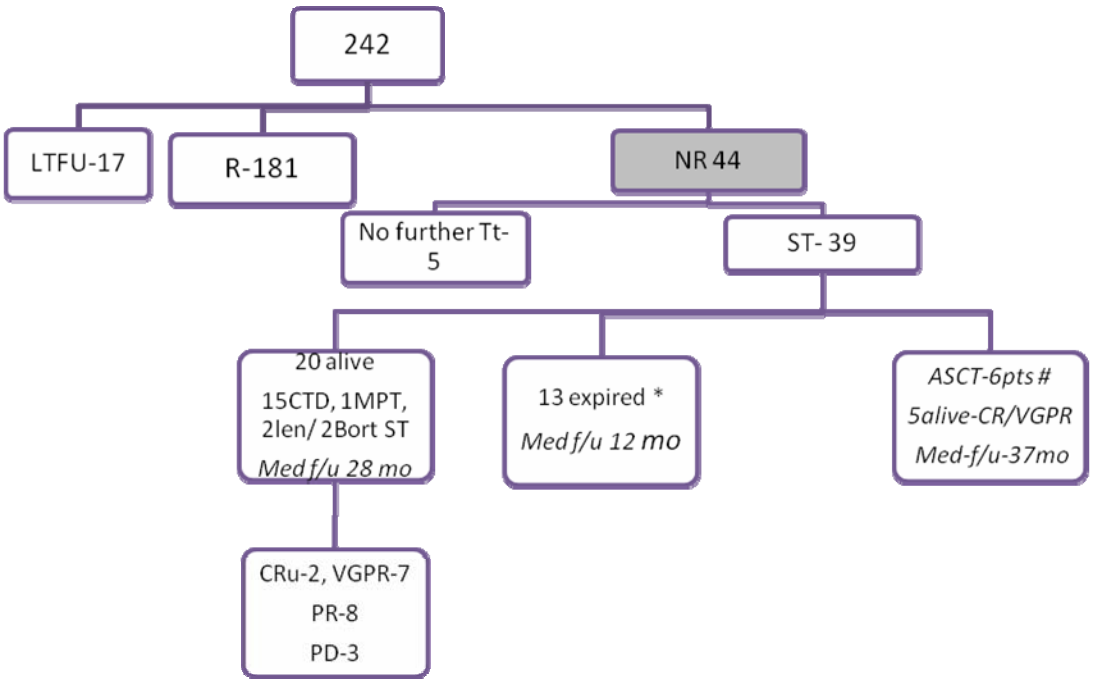

Figure. 6: Flow chart depicting the response to Thalidomide – Dexamethasone and subsequent course of NR. R-Responder, NR-Non responder, LTFU-Lost to follow up, PD-Progressive disease, mo-months, med f/u- Median follow up, PD-Progressive disease, Cyclo-Dex- Cyclophosphamide + Dexamethasone, Cyclo-Pred- Cyclophosphamide + Prednisolone, CTD- Cyclophosphamide + Thalidomide + Dexamethasone, MP-Melphalan + Prednisolone, MPT – Melphalan + Prednisolone + Thalidomide, LD – Lenalidomide + Dexamethasone, LLD – Lenalidomide + Pegylated Liposomal Doxorubicin + Dexamethasone, PAD – Bortezomib + Adriamycin + Dexamethasone,ST-Salvage therapy, Tt-Treatment, CR-Complete remission, CRu-Complete response unconfirmed, VGPR-Very good partial response, PR-Partial response.

*Salvage Therapy of 13 expired patients - 1 len/1 Bort, 5CTD, 4 CD, 2 MPT

Salvage therapy of patients undergoing ASCT- Bort/Len-6, 1 Expired (PD) -23 mo

Progression free survival

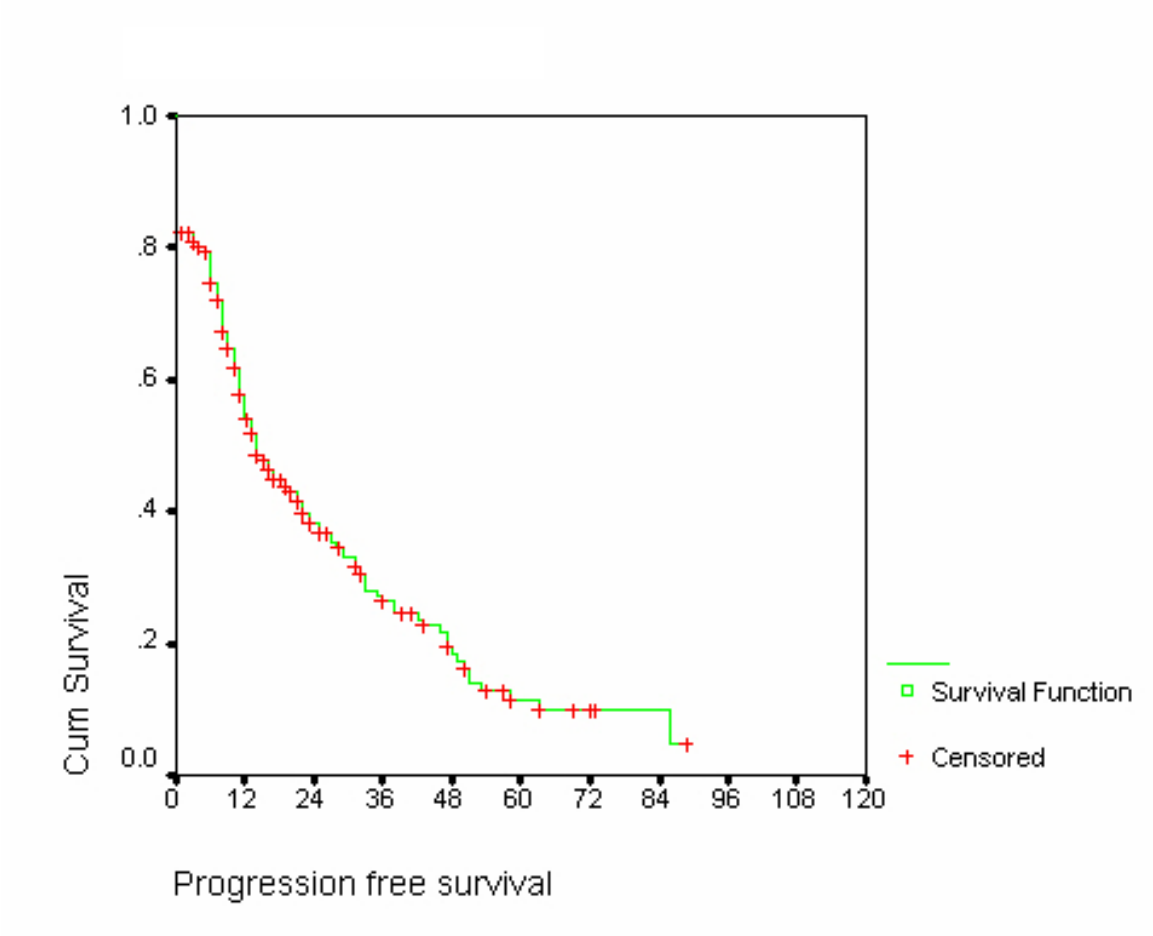

Figure-7. Kaplan Meier curve of Progression free survival (PFS) of the entire cohort of 225 patients available for analysis. Events (Progressive disease/Relapse) -153, Mean PFS -25.5 months and Median PFS -14 months (95%CI-10.7 to 17.2). The PFS at 24 and 36 months are 38.3 months and 26.3 months respectively.

Overall survival

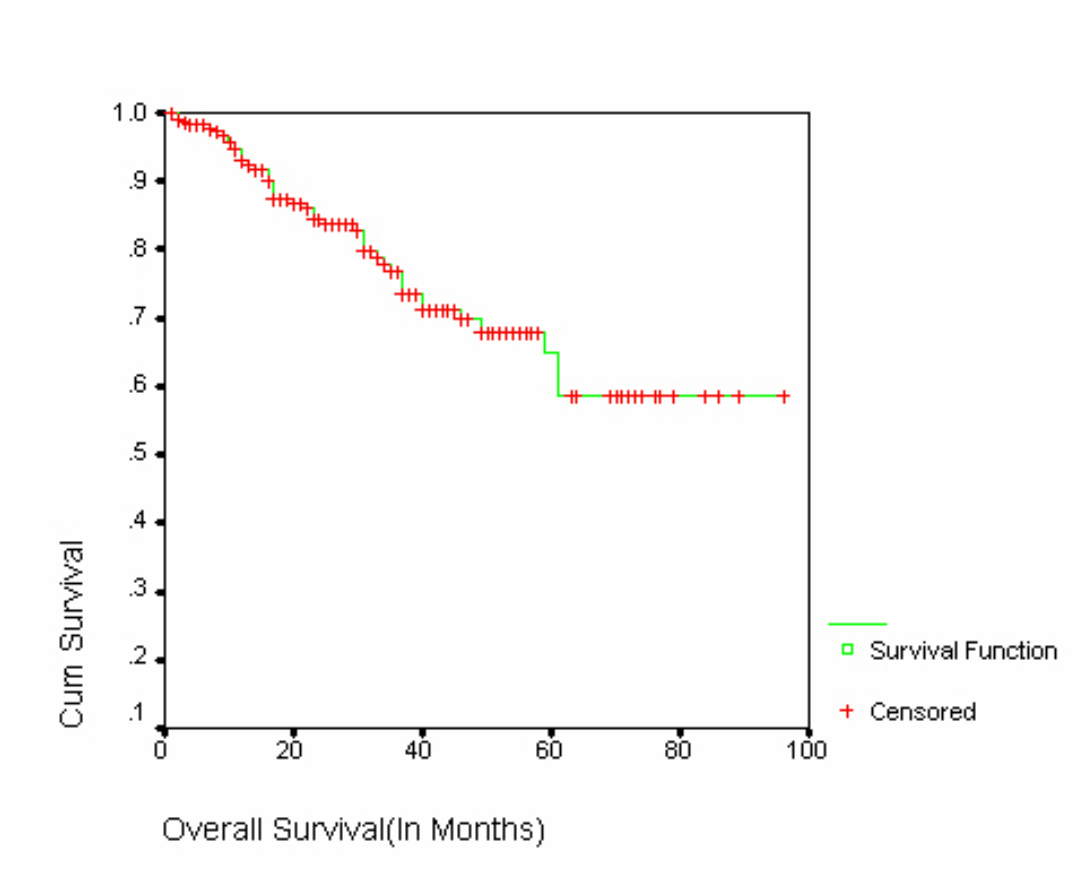

Figure-8. Kaplan Meier curve for overall survival(PFS) of the entire cohort of 225 patients available for analysis. Events (Death) -45, Median - not reached, Mean OS -70 months (95%CI- 64 to 77). The OS at 24 and 36 months are 84.5 months and 76.9 months respectively. Median f/u -24mo (1-96 months)

Progression free survival

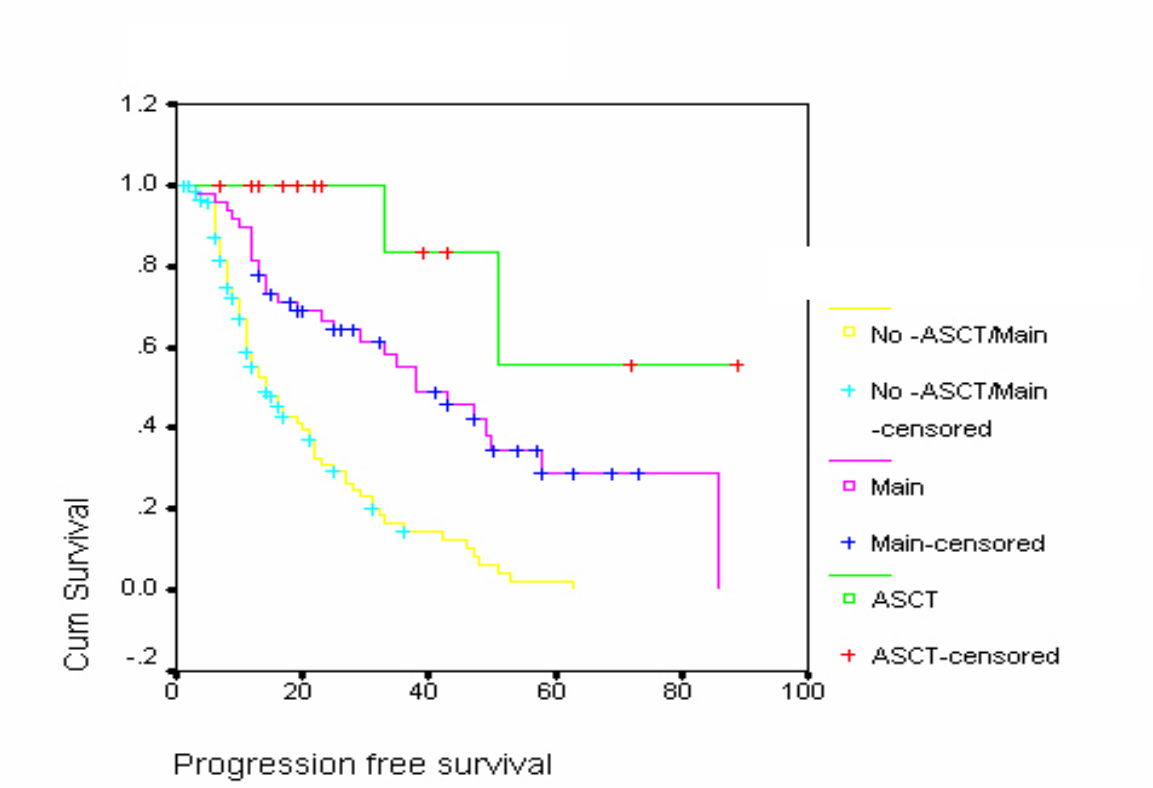

Figure-9. Kaplan Meier curve for progression free survival (PFS) of the three groups: ASCT- 13 pts. (Green), Maintenance – 49 pts. (Pink) and No ASCT/No Maintenance - 119 pts. (Yellow). Events (Progressive disease).Median - not reached in the ASCT group and the mean PFS was 69.1 months (95% CI – 47.8 to 90.3). The median PFS for the Maintenance group was 38 months (95%CI-23.4 to 52.5). The median PFS for the No ASCT/ No Maintenance group was 14 months (95%CI-9.9 to 18.06). The PFS at 24 and 36 months were 100% & 83.3%, 66.6% & 55.1% and 31% & 14.7% in the ASCT, Maintenance and No ASCT/No Maintenance groups respectively. *p*=0.0000

Overall Survival

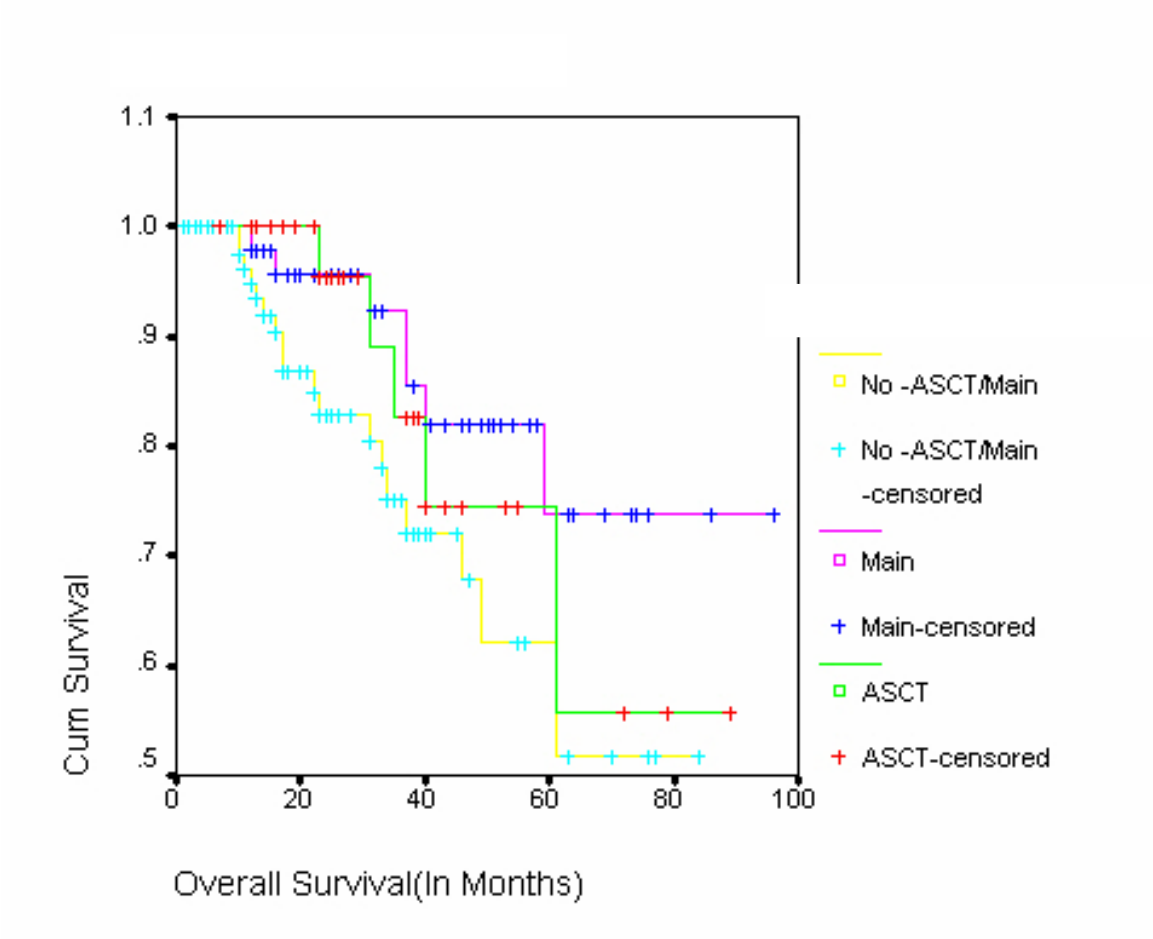

Figure 10. Kaplan Meier curve for overall survival (OS) of the three groups: ASCT- 29 pts. (Green), Maintenance – 48 pts. (Pink) and No ASCT / No Maintenance - 110 pts. (Yellow). Events (Death) (**ASCT- 5, Maintenance – 7 and No ASCT / No Maintenance – 18.)** Median - not reached in all the three groups. The OS at 24 and 36 months in the three groups were 95.45% & 82.73%, 95.6% & 92.4% and 82.96% & 75.23% in the ASCT, Maintenance and No ASCT/No Maintenance groups respectively. *p*=0.1064

Tables

Table-1.Incidence of Presenting Symptoms in Patients with Multiple Myeloma

Symptom	Incidence (%)
Bone pain (especially back pain)	58
Fatigue (typically caused by anemia)	32
Pathologic fracture	26 to 34
Weight loss	24
Paresthesias	5
Fever	0.7
None (asymptomatic)	34
Anaemia	73
Renal failure	19
Hypercalcemia	13

Table-2. IMWG criteria for diagnosis of Myeloma.

MGUS	Asymptomatic myeloma	Symptomatic myeloma
M-protein in serum <30 g/l	M-protein in serum >30 g/l and/or Bone marrow clonal plasma cells >10 %	M-protein in serum and/or urine**
No related organ or tissue impairment ((no end organ damage including bone lesions)		Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma
No related organ or tissue impairment ((no end organ damage including bone lesions)	No related organ or tissue impairment (no end organ damage including bone lesions) or symptoms	Myeloma-related organ or tissue impairment (including bone lesions)

MGUS-Monoclonal gamopathy of undetermined significance *If flow cytometry is performed, most plasma cells (> 90%) will show a neoplastic phenotype. Some patients may have no symptoms but have related organ or tissue impairment. The European Myeloma Network has provided a practical guidance on the optimal methods for flow cytometry(49).
** No specific concentration required for diagnosis. A small percentage of patients have no detectable M-protein in serum or urine but do have myeloma-related organ impairment (ROTI) and increased bone marrow plasma cells (non-secretory myeloma)

Table-3 - Myeloma-related organ or tissue impairment (ROTI)(4)

Clinical effects due to myeloma	Definition
***Increased calcium levels**	Corrected serum calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
***Renal insufficiency**	Creatinine>173mmol/l (2mg/dl)
***Anaemia**	Haemoglobin 2 g/dl below the lower limit of normal or haemoglobin <10 g/dl
***Bone lesions**	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

*CRAB (calcium, renal insufficiency, anaemia or bone lesions).

Table-4. Phase II and Phase III trials of Thalidomide combination therapy in newly diagnosed MM.

Regimen (No. Of pts)	Response After induction		Response After ASCT		PFS	OS	Ref.
	CR+PR	CR/≥VGPR	CR+PR	CR/≥VGP			
TD (50) Phase II	64	-/30	NR	NR	NR	NR	(82)
T(28) vs. TD(40) PhII	36 72	NR NR	NR NR	NR NR	NR NR	NR NR	(83)
TD (71) PhII	66	8/17	NR	NR	NR	NR	(84)
TD (100) vs. VAD(100)	76 52	10/19 8/14	NR NR	NR NR	NR NR	NR NR	(80)
TD (103) vs. VAD(104)	63 41	4/NR 0/NR	NR NR	NR NR	NR NR	NR NR	(81)
TD (100) VS DEX (104) Pl	66 52	NR/35 NR/13	68 62	NR/44 NR/42	NR NR	NR NR	(11)
TD(235) vs. DEX(235) Ph III	63 46	7.7/43.8 2.6/15.8	NR NR	NR NR	Median TTP 6.5	NR NR	(85)
TAD(268) vs. VAD (268)	71 57	3/37 2/18	84 76	14/54 12/44	Median,34m Median,22m *P=0.001*	Median,73 Median,60 *P=0.77*	(86)
TD(145) MP(144)	68 50	2/13 2/26	NR NR	NR NR	TTP-21.2 29.1	Med-41.5 49.4	(87)
TT 2 + Thal (	NR	NR	NR	62/NR	5YR, 56%	5YR, 65%	(88)
TT no Thal(3	NR	NR	NR	43/NR	5YR, 44% *P=0.01*	5YR, 65% *P=0.9*	

ASCT-Autologous stem cell transplantation, PFS-Progression free survival, OS-Overall survival, CR-Complete response, PR-Partial response, VGPR-Very good partial response, TD-Thalidomide+Dexamethasone, VAD-Vincristine+Adriamycin+Dexamethasone, DASCT-Double Autologous stem cell transplantation, NR-Not reported, TTP-Time to progression, TAD-Thalidomide+Adriamycin+Dexamethasone, Dexa-Dexamethasone, TT-Total therapy, Thal-Thalidomide, mo-months.

Table 5. Thalidomide Maintenance Trials

Trial/year	Study design	PFS/EFS	OS	Ref
Offidani et.al. 2009	Thal + Dex vs. IFN + Dex	**2 yr** **63% vs. 32% (p=0.024)**	2 yr 84% vs. 68% (p=0.03)	**(12)**
Ludwig, H. et al. **2010**	Thal+IFN vs. INF	**27.7m vs. 13.2m** **(p=0.0068)**	52.6m vs. 51.4m (p=0.81)	**(13)**
Attal, et al. 2006.	A-no therapy vs. B-pamidronate vs. C- P+T	**3 yr EFS** **52 % vs. 36%** **(p<0.009)**	4 yr 87% vs. 75% (p<0.04)	(90)
Spencer, et al. **2009**	AP vs. AP+T	**3 yr PFS** **42 % vs. 23%** **(p<0.001)**	3 yr 86% vs. 75% (P<0.0045)	(91)
Lokhorst, et al. 2010	VAD vs. TAD for induction INF vs. T for maintenance	**Median EFS** **34m vs. 22m** **(p<0.001)**	median 73m vs. 60m (p=0.77)	(86)

PFS-Progression free survival, OS-Overall survival, EFS-Event free survival, Thal + Dex-Thalidomide+Dexamethasone, IFN + Dex-Interferon+Dexamethasone, Thal+IFN-Thalidomide+Interferon, IFN-Interferon, P+T-Pamidronate+Thalidomide,VAD-Vincristine+Adriamycin+Dexamethasone,TAD-Thalidomide+ Adriamycin +Dexamethasone, AP-,AP+T-+Thalidomide, m-months

Table - 6. International Myeloma Working Group uniform response criteria: CR and other response categories (89)

Response subcategory	Response criteria[a]
Scr	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level o100mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200mg per 24 h If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 44:1 or o1:2.

Table-7. International Myeloma Working Group uniform response criteria: disease progression and relapse (89)

Relapse subcategory	Relapse criteria
Progressive disease To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ≥25% from baseline in Serum M-component (the absolute increase must be X0.5 g/dl) and/or Urine M-component (the absolute increase must be ≥200mg/24 h) and/or Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10mg/dl. Bone marrow plasma cell percentage: the absolute % must be >10% Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue Plasmacytomas. Development of hypercalcemia (corrected serum calcium >11.5mg/dl or 2.65mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (411.5mg/dl) [2.65mmol/l] 4. Decrease in hemoglobin of X2 g/dl [1.25mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2mg/dl or more [177 mmol/l or more]
Relapse from CRa (To be used only if the end point studied is DFS)	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of >5% plasma cells in the bone marrow Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.

All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.

For progressive disease, serum M-component increases of ≥1 gm/dl are sufficient to define relapse if starting M-component is ≥5 g/dl.

Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Table-8.Baseline demographics

Age distribution	No.
Total	242
Range	21 to 80 yrs
Median	54 yrs
Mean	53.38 yrs
Age <65	219(90.4%)
Age >65	23(9.6%)
Age>50	158(65.3%)
Age<50	84(34.7%)
Sex distribution	
Males	172(71.1%)
Females	70(28.9%)
M:F	2.45:1

Table-9. Presenting Features

Presentation	No.	%
Anaemia	143	59.1
Renal failure*	51	21.1
Weight loss	16	6.6
Symtoms related to bone involvement		
Back pain	*139*	*57.4*
Cord compression/ paraparesis	*17*	*7*
Pathological fractures	*13*	*5.3*
Humerus	*6*	
Femur	*4*	
Clavicle	*1*	
Ulna	*1*	
Acetabulum	*1*	
Fever	*12*	*4.9*
Symptomatic hypercalcemia	*7*	*2.8*
Bleeding	*5*	*2.06*
Infection	*7*	*2.8*
UTI	*5*	
Pneumonia	*1*	
Diarrhoea	*1*	
Peripheral neuropathy	2	0.8
Polyarthritis	2	0.8
Ureteric/renal calculi	2	0.8
Proptosis	1	0.4
Lymphadenopathy	1	0.4
DVT#	1	0.4

*Renal failure is defined as Sr. Creatinine ≥2mg/dl.
#Deep vein thrombosis

Table-10.Baseline Characteristics

Baseline characteristics	No. (%)
Haemoglobin , Median-(n=242)	9.3 g/dl (3.3 – 16.8 g/dl)
Hb <10g/dl (%)	143(59.1%)
Hb ≥10g/dl (%)	99(40.9%)
Thrombocytopenia (Plt<100000/cu.mm) (n=242)	16(6.6%)
Leukopenia (WBC < 4000/cu.mm) (n=242)	8(3.3%)
Sr.Creatinine, Median (n=242)	1.1mg/dl (0.6 -21.3mg/dl)
Cr <2mg/dl	0.6 -21.3 mg/dl
Cr >2mg/dl	51(21.1%)
Sr.Calcium, Median (n=242)	9.0 mg/dl(6-14.6mg/dl)
Ca <10.5mg/dl	194(80.2%)
Ca ≥10.5mg/dl	48(19.8%)
Sr.Albumin, Median (n=240)	3.55g/dl(1.0-5.5g/dl)
Alb <3.5g/dl	112(46.7%)
Alb ≥3.5g/dl	128(53.3%)
B2 microglobulin, median, (n=210)	4.5(0.4-38)
<3.5	75(35.7%)
≥3.5 <5.5	47(22.4%)
≥5.5	88(41.9%)

Hb-Haemoglobin, Cr-Creatinine, Ca-Calcium, Alb-Albumin

Table-10.Baseline characteristics continued

Baseline characteristics	No. (%)
Sr.Uric acid, median (n=165)	6.6mg/dl(0.2-16.3)
>7mg/dl (Elevated)	73(44.2%)
Sr.LDH, median (n=182)	348 u/dl(0-1138)
>460 u/dl (Elevated)	38(20.9%)
Urine BJP, (n=228)	
Positive	145(63.6%)
24 Hour urine protein, median (n=142)	0.949g/day(0-14.9)
≥200mg/day	107(75.4%)
Type of myeloma (n=242)	
Heavy chain	187
IgG	135(55.7%)
IgA	32(13.2%)
IgM	4(1.6%)
Unknown	16(6.6%)
Biclonal	8(3.3%)
Light chain	44(18.2%)
Nonsecretory	3(1.2%)
BM % plasma cells <50%	**62 (25.6)**
>50%	**180(74.4)**
M band Quantification	
≤3 g/dl	**109(45)**
>3 to ≤5g/dl	**71(29.3)**
>5 to ≤7g/dl	**38(15.7)**
>7g/dl	**24(9.9)**

LDH-Sr.Lactate dehydrogenase, Urine BJP-Urine Bence Jones Protein.

Table-11.Bone involvement

Bone involvement (n-=242)	No. (%)
Present	200(82.6%)
Lytic lesions	134(55.3%)
Wedge compression fracture of vertebrae	116(47.9%)
Pathological fractures of long bones	13(5.3%)
Plasmacytoma	57(23.6%)
Single Bony Plasmacytoma	*41*
Extramedullary Plasmacytoma	*6*
Orbit	*2*
Nasopharynx	*1*
Lung Parenchyma	*1*
Pleura	*1*
Left supraclavicular node	*1*
Multiple Plasmacytomas	*10*
Osteopenia	29(11.9%)
Sclerotic lesion	2(0.8%)

Table-12.Progression from MGUS/ Solitary Plasmacytoma

	No.	Time to Progress (mo)
MGUS	1	52
Solitary Plasmacytoma	5	Mean-52(Range: 44-65)

MGUS-Monoclonal gamopathy of undetermined significance

Table-13.Staging

ISS (n=209)	No. (%)
I	53(25.4%)
II	68(32.5%)
III	88(42.1%)
DSS (n=242)	**No. (%)**
I	31(12.8%)
IA	30
IB	1
II	86(35.5%)
IIA	73
IIB	13
III	125(51.7%)
IIIA	89
IIIB	36

ISS-International staging system, DSS-Durie-Salmon Staging

A-Sr.Creatinine <2mg/dl, B-Sr.Creatinine ≥2mg/dl

Table-14. Thalidomide-Dexamethasone-Treatment characteristics

Thalidomide-dexamethasone No. of Cycles	N=225(17 pts lost to f/u)
Median no. of cycles-7(Range-1 to 27)	
Mean no. of cycles-8	
Thalidomide dose	**No. (%)**
Median dose-200mg OD (range-50mg to 400mg OD)	
Mean dose-159.5mg OD	
≤100mg/day	87(36)
>100mg up to 200mg/day	153(63.2)
>200mg/day	2(0.8)
Dexamethasone dosage	
Median: 40 mg OD (Range: 8 – 40 mg OD)	
Mean: 31.45 mg OD	

OD-Once daily

Table-15.DVT prophylaxis

DVT Prophylaxis	Number Total-242
Aspirin 75mg	217
Sintrom*	1
Clopidogrel	1
Nil	23

DVT-Deep vein thrombosis

*Developed DVT at diagnosis and hence initiated on Sintrom

Table-16.Biphosphonate use

Biphosphonate use	Number Total-242
Yes	173(71.5%)
No	69(28.5%)

Table-17. Initial response to TD

Total no. of patients initiated on TD	**242**
Lost to follow up	17
No. of patients available for response assessment	225
CR	10(4.5%)
CRu	10(4.5%)
VGPR	70(31.1%)
PR	91(40.4%)
NR	44(19.5%)
No. of patients responding to TD	181(80.5%)
≥VGPR	90(40.1%)
PR	91(40.4%)
Median Time to respond	3mo (1-13 mo)
No. of patients progressed post TD	153(68%)
Time to progress after initiation of TD	
Median	11 months(1-86)
Mean	10 months

TD-Thalidomide-Dexamethasone, CR-Complete remission, Cru-Complete response unconfirmed, VGPR-Very good partial response, PR-Partial response, NR-No response, mo-months

Table-18. Response to TD according to ISS and DSS

ISS	CR/Cru	VGPR	PR	NR
I (n– 53)	6(11.3%)	14(18.8%)	23(43.4%)	8(15.1%)
II (n-68)	7(10.2%)	20(29.4%)	24(35.2%)	13(19.1%)
III (n-88)	4(4.5%)	29(32.9%)	28(31.6%)	16(18.9%)
DSS				
I (n-31)	2(6.4%)	5(16.1%)	15(48.3%)	8(25.8%)
II (n-86)	6(6.9%)	28(32.5%)	35(40.6%)	14(16.2%)
III (n-125)	12(9.6%)	37(29.6%)	41(32.8%)	22(17.6%)

TD-Thalidomide-Dexamethasone, ISS-International staging system, DSS-Durie-Salmon Staging, CR-Complete remission, CRu-Complete response unconfirmed, VGPR-Very good partial response, PR-Partial response, NR-No response.

Table-19.Overall Survival according to ISS/DSS

ISS	Alive at last f/u no. (%)	Median f/u, (range)
I (n=51)	46(90.1)	22.5 mo (3-74 mo)
II (n=64)	51(79.6)	26 mo (4-89 mo)
III (n=77)	56(72.7)	28 mo (1-86 mo)
DSS	**Alive at last f/u no.(%)**	**Median f/u, (range)**
I(n=30)	26(86.6)	20 mo (5-76 mo)
II (n=83)	66(79.5)	25 mo (1-96 mo)
III (n=112)	88(78.5)	25.5 mo (3-89 mo)

ISS-International staging system, DSS-Durie-Salmon Staging, f/u-follow up, mo-month(s)

Table-20. Thalidomide maintenance post TD induction

Duration of Thalidomide maintenance post induction	
No. of patients receiving maintenance therapy*	49
Range	2-69 months
Median	8 months
Mean	14 months
Dose of Thalidomide during maintenance	
Median dose	100mg OD (50 -200)

TD-Thalidomide-Dexamethasone, *1 patient received Lenalidomide maintenance.

Table-21. Deep vein thrombosis & pulmonary embolism

Site of Thrombosis	**Thalidomide continued (Yes/No)**
Right common iliac, external iliac and common femoral vein	No
Chronic pulmonary thromboembolism	No
Left common iliac, external iliac, common femoral and superficial femoral veins	Yes
CVT[#]	Yes
Chronic DVT of left common femoral vein*	Yes
B/L infra renal IVC, right external iliac veins	Yes
Left common femoral vein[$]	Yes

*presentation at diagnosis,

[$]Polycythemia vera - JAK 2 mutation positive

[#]Not on aspirin prophylaxis

DVT-Deep vein thrombosis, CVT-Cortical venous thrombosis and IVC-Inferior Vena Cava.

Table-22. Adverse effects of Thalidomide-Dexamethasone

Adverse effects	Number(%) Total-225
Neuropathy	48(21.3)
Constipation	50(22.2)
Somnolence	5(2.1)
Rash	5(2.1)
DVT	6(2.6)
Hyperglycemia	28(12.4)
Infection	4(1.5)
Grade 4 myopathy	1(0.4)
Depression	1(0.4)
Cushings syndrome	1(0.4)
syncope	1(0.4)
Seizures	1(0.4)
Pancreatitis	1(0.4)
Neutropenia	1(0.4)

DVT-Deep vein thrombosis

Table-23.Autologous stem cell transplantation characteristics

Total no. of ASCT – 29	**Median(range)**
Upfront post TD induction-13	
Post relapse/Progressive disease-16	
Median age, (range)	50yrs(29-59)
Median time from diagnosis to ASCT, mo	12 (range:4-32)
No. of prior chemotherapy regimens	
One	13
Two	11
Three	5
Melphalan dose, median mg/m^2	200(100-200)$^{\$}$
Cell dose	
CD 34 x 10^6 cells/kg	3.8(1.15-17)
MNC x 10^8 cells/Kg	6.1(1.54-19.64)
Mucositis	
Grade I	2
Grade II	4
Grade III	20
Grade IV	3
Time to ANC >500/cu.mm, days	11(10-13)
Time to ANC >1000/cu.mm, days	12(10-14)
Time to platelet >20000/cu.mm, days	12(8-33)
G-CSF Support, days	6(4-16)

Table-23. Autologous stem cell transplantation characteristics –continued	
No. of days of fever	3(1-16)
No. day of antibiotics	12(5-21)
Duration of f/u post ASCT, months	15(1-74)
No. pts with progressive disease post ASCT	11
Time to progress post transplant, months	13(2-44)
No. of patients with post transplant maintenance	14
Thalidomide	11
Lenalidomide	3
Dose of Thalidomide, mg OD	100(100-200)
Duration of maintenance, months	10(2-30)
Pre-ASCT Status of Myeloma	
CR/CRu	9
VGPR	11
>VGPR	20
PR	6
Post-ASCT Status of Myeloma	
CR/CRu	15
VGPR	8
>VGPR	23
PR	5
PD	1

TD-Thalidomide-Dexamethasone, CR-Complete remission, CRu-Complete response unconfirmed, VGPR-Very good partial response, PR-Partial response, PD-progressive disease, MNC-Mononuclear cell count, ANC-Absolute neutrophil count,G-CSF-Granulocyte colony stimulating factor,ASCT-Autologous stem cell transplantation, mo-months.

Table-24. Second line therapy

No.of patients changed to second line therapy	**143**
Time to second line therapy	
Median (range)	9 months (1-63)
Mean	15 months
Second line therapy post relapse/ PD	No. (%)
Cyclo-Dex/Cyclo-Pred	15(10.4%)
CTD	89(62.2%)
MP/MPT	12(8.3%)
LD/LLD	7(4.8%)
PAD	10(7%)
TD	8(5.5%)
DVD	1(0.7%)
HDD	1(0.7%)

PD-Progressive disease, Cyclo-Dex- Cyclophosphamide + Dexamethasone, Cyclo-Pred- Cyclophosphamide + Prednisolone, CTD- Cyclophosphamide + Thalidomide + Dexamethasone, MP- Melphalan + Prednisolone, MPT – Melphalan + Prednisolone + Thalidomide, LD – Lenalidomide + Dexamethasone, LLD – Lenalidomide + Pegylated Liposomal Doxorubicin + Dexamethasone, PAD – Bortezomib + Adriamycin + Dexamethasone, TD – Thalidomide + Dexamethasone. DVD – Doxorubicin, Vincristine, Dexamethasone, HDD – High dose dexamethasone.

Table 25. Statistical analysis

Variable	Resp vs. No resp	≥VGPR vs. PR	PFS	OS	Post ASCT Response
Age	0.767	0.274	0.684	0.607	-
Sex, M vs. F	1.000	1.000	0.173	0.461	0.182
Thalidomide Dose ≤100 vs. >150- 200 vs. >200mg	0.780	0.114	0.256	0.148	0.208
Hb <10 vs. ≥10g%	0.867	0.474	0.195	0.45	0.301
Ca <10.5 vs. >10.5mg%	0.533	0.371	0.288	1.000	0.710
Cr <2 vs. >2 mg%	0.675	0.577	0.110	0.216	0.889
Bone involvement **Y vs. N**	0.380	0.842	0.853	1.000	0.546
Plasmacytoma Y vs. N	0.847	0.232	1.000	1.000	0.196
BM % Plasma cells **<50, >50**	0.704	0.498	0.327	1.000	0.546
M Band level <3, 3-5, **5-7, >7**	0.384	0.601	0.617	0.858	0.471
Myeloma type **Heavy chain vs. light chain+Non secretory**	0.130	0.071	0.715	0.671	0.182
Ur BJP Positive / Negative	0.486	1.000	0.650	0.860	1.000
24 hr urine protein <200, >200mg/d	0.110	1.000	0.658	1.000	1.000
ISS	0.749	0.728	0.071	0.055	0.709
DSS	0.510	0.163	0.967	0.610	0.601
CR+CRu vs. VGPR vs. PR	-	-	***0.000***	0.232	-
ASCT vs. Maint. Vs. No ASCT/Maint	-	-	***0.0000***	0.1064	-

TD-Thalidomide-Dexamethasone,CR-Complete remission, CRu-Complete response unconfirmed,VGPR- Very good partial response, PR-Partial response, OS-Overall survival, PFS-Progression free survival, BJP- Bence Jones Protein, ASCT-Autologous stem cell transplantation, ISS-International staging system, DSS-Durie Salmon staging,

Table 26. Comparison of various TD trials with the present study.

Regimen (No. Of pts)	After induction		After ASCT		PFS	OS	Ref.
	CR+PR%	CR/≥VGPR%	CR+PR %	CR/≥VGPR%			
TD (50) Phase II	64	-/30	NR	NR	NR	NR	(81)
T(28) vs. TD(40) PhII	36 72	NR NR	NR NR	NR NR	NR NR	NR NR	(82)
TD (71) PhII	66	8/17	NR	NR	NR	NR	(83)
TD (100) vs. VAD(100)	76 52	10/19 8/14	NR NR	NR NR	NR NR	NR NR	(79)
TD(103) vs. VAD(104)	63 41	4/NR 0/NR	NR NR	NR NR	NR NR	NR NR	(80)
TD (100) VS DEX (104) Ph III	66 52	NR/35 NR/13	68 62	NR/44 NR/42	NR NR	NR NR	**(11)**
TD(235) vs. DEX(235) Ph III	63 46	7.7/43.8 2.6/15.8	NR NR	NR NR	Median TTP22.6 6.5	NR NR	(84)
TAD(268) vs. VAD (268)	71 57	3/37 2/18	84 76	14/54 12/44	Median,34mo Median,22mo *P=0.001*	Median,73mo Median,60mo *P=0.77*	**(86)**
TD(145) MP(144)	68 50	2/13 2/26	NR NR	NR NR	TTP-21.2 29.1	Med-41.5 49.4	(91)
TT 2 + Thal (323 TT without Thal(	NR NR	NR NR	NR NR	62/NR 43/NR	5YR, 56% 5YR, 44% *P=0.01*	5YR, 65% 5YR, 65% *P=0.9*	(85)
D ASCT + TH vs. DASCT+NoThal((retrospective case-matched stu	NR NR	NR/30 NR/15	NR NR	NR, 68% NR, 49%	4YR, 51% 4YR, 31% *P=0.001*	5YR, 69% 5YR, 53% *P-0.07*	(93)
Present study(22 TD	80.4	40/8.8	13 upfront 100	92.3	36 Months ASCT-83.3% MAIN-55.1% NIL-14.7% P=0.000	36 Months ASCT- 82.7% MAIN- 92.4% NIL- 75.2% P=0.1064	

ASCT-Autologous stem cell transplantation, PFS-Progression free survival, OS-Overall survival, CR-Complete response, PR-Partial response, VGPR-Very good partial response, TD-Thalidomide+Dexamethasone, VAD-Vincristine+Adriamycin+Dexamethasone, DASCT-Double Autologous stem cell transplantation, NR-Not reported, TTP-Time to progression, TAD-Thalidomide+Adriamycin+Dexamethasone, Dexa-Dexamethasone, TT-Total therapy, Thal-Thalidomide, mo-months, MP – Melphalan-Prednisolone, ASCT – Autologous stem cell transplantation group, Maint – Thalidomide maintenance group, NIL – No Autologous stem cell transplantation and no maintenance Thalidomide group,

Proforma

- Age:
- Sex:
- Address:
- Date of Diagnosis:
- Base line Characteristics
  - CBC profile
  - Sr.Cr
  - Sr.Ca
  - Total Protein
  - Sr.Albumin
  - LDH
  - B2 microglobulin
  - M Band
  - Urine BJP
  - 24 hour urine Protein
  - Sr.Free Light Chain Assay
  - Sr.Immunofixation Electrophoresis
  - Skeletal survey
  - Bone marrow plasma cell %
  - DSS/ISS staging
- Date of Initiation of therapy
- Treatment outcome
  - Response status at follow up visit

- Duration of treatment
- Maximum Tolerated doses of
    - Thalidomide
    - Dexamethasone
- Adverse effects
- Time to response
- Time to progression
- Time to Change therapy
- Time to transplant
- Status at last visit

- **Maintenance** yes/no
    - Date of initiation
    - Dose
    - Duration
    - Time to progress
    - Time to change therapy
    - Status at last visit

- **ASCT** Yes/No
    - Date of transplant
    - Melphalan Dose
    - Pretransplant status of disease

- Post transplant status of disease
- Cell dose
- Engraftment
    - ANC >500
    - Platelet count >20000
- Infection
- Mucositis
- Post Transplant maintenance
- Time to relapse/Progress
- Status at last visit

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MASTER CHART

Expansion of codes used in Master chart

SAD	Symptoma at diagnosis	RES	Best response to TD
DOD	Date of diagnosis	PD	Progressive disease
AGE	Age at diagnosis	TTP	Time to progression
DOS	Duration of symptoms in months	ADD Tt	Number of additional therapiestherapy
SP/M	Past history of solitary plasmacytoma or MGUS	STATUS	Status of myeloma at last contact
Hb	Haemoglobin	A/D/L	Alive, Dead or lost to follow up at last contact
PL	Platelets	Last VISIT	Date of last visit
TC	Total WBC count	2nd TT	Second line therapy
Ca	Serum Calcium	Maint	Thalidomide maintenance
Cr	Serum Creatinine	START MAINT	Date of starting maintenance post TD
ALB	Serum Albumin	STOP MAIN	Date of stopping maintenance post TD
Bone	Bone involvement	Main Do	Maintenance Thalidomide dose
PCM	Plasmacytoma	DVT	Deep vein thrombosis
UA	Serum Uric acid	ABMT	Autologous bone marrow transplant
LDH	Serum Lactate dehydrogenase	TTT	Time from diagnosis to transplant
M	M band	Pre Tx	Status of myeloma pretransplant
BM%	BM plasma cell %	NOC	Number of prior chemotherapies pre transplant
B2M	Beta 2 microglobulin	Mel	Melphalan dose
ISS	International staging system	MUC	Grade of Mucositis
DSS	Durie Salmon staging	MNC	Mono nuclear cell dose
BJP	Urine Bence Jone Protein	CD34	CD 34 cell dose
24HUP	24 hour urine protein	ANC1	No. of days to ANC increase >500
MM	Type of Multiple Myeloma	ANC2	No. of days to ANC increase >1000
THAL START	Date of starting TD	PL1	No. of days to platelets >20000
THAL STOP	Date of stopping TD	GCSF	No. of days of GCSF support
DOT	Thalidomide dose	Fever	No. of days of fever post transplant
DDO	Dexamethasone dose	ABD	No. of days of antibiotics
CY	Number of cycles of TD	PTS	Post ASCT status of myeloma
ASP	Aspirin prophylaxis	PTPD	Post transplant progressive disease
BIP	Bisphosphonate	PTRD	Post transplant relapse date
PN	Peripheral neuropathy	PTM	Post ASCt maintenance
CON	Constipation	PTMD	Post transplant maintenance duration
SOM	Somnolence	PTMDo	Post transplant maintenance dose of Thalidomide

TTR	Time to respond to TD	LTF	Lost to followup
PR	Partial response	VGPR	Very good partial response
NR	No response	CR	Complete response
CRu	Complete response unconfirmed	TD	Thalidomide dexamethasone

Interpretation of codes used for individual parameters

SAD – Symptoms at diagnosis 1-Anaemia 2-LBA 3-Renal Failure 4-Hypercalcemia 5-Fever 6-Infection 7-Paraparesis 8-Wt loss 9-Pathological fracture of long bone 10-Renal/Ureteric calculus 11-Peripheral neuropathy 12-Supraclavicular lymphadenopathy 13-Bleeding 14-Plasmacytoma 15-Polyarthritis 16-DVT	Second line therapy CP – Cyclophosphamide + Prednisolone CD - Cyclophosphamide + Dexamethasone TD – Thalidomide + Dexamethasone MP – Melphalan + Prednisolone MPT - Melphalan + Prednisolone + Thalidomide LD – Lenalidomide + Dexamethasone LLD - Lenalidomide + Dexamethasone + Pegylated lipodoxorubicin PAD – Bortezomid + Adriamycin + Prednisolone DVD – Doxorubicin + Vincristine + Dexamethasone HDD – High dose dexamethasone
Hb 1 <10 g/dl 2≥10 g/dl	Dose of Thalidomide 1 - ≤100 mg per day 2 - >100mg to ≤200mg per day 3 - >200mg per day
PL 1<100000/cu.mm 2≥100000/cu.mm	ISS 4-Not available
TC - WBC COUNT 1<4000/cu.mm 2≥4000/cu.mm	Urine BJP 1-POS 2-NEG 3-ND
Sr. Creat 1 - Cr<2 2- Cr>=2 3-NA/ND	24 Hour urine protein 1-<200 2>200 3-ND
Bone lesions 1- Present 0- Absent	ASP prophylaxis Y – ASPIRIN N – NO C – Clopidogrel S – Sintrom
LDH	UA

N-NORMAL-<=460 H-ELEVATED->460 NA-Not available	N-NORMAL <=7 H-ELEVATED >7 NA- Not available
AE – Adverse effect of Thalidomide Dexamethasone 0 – No 1 – Yes 1 – Hyperglycemia 2 – Cushing syndrome 3 – Grade IV myopathy 4 – Infection 5 – Somnolence 6 – Neutropenia 7 – Rash	Maint – Post TD induction therapy of patients a-ASCT b- Thalidomide maintenance c-no ASCT no main d-lost to f/u or non responders to TD

0.00	Sex	DOD	AGE	SAD	SP/M	DOS	Hb	PL	TC	Ca	ALB	Cr	BONE	PCM	LDH	UA	BM%	B2M	DSS	ISS	M Band	MM	BJP	24HUP	ASP	BIP	THAL START	THAL STOP	CY	DOT	DDO	PN
1	M	01/03/2009	55	2	0	3	2	2	2	1	2	1	1	N	NA	NA	1	1	1A	1	0	5	1	3	Y	Y	01/03/2009	05/27/2009	5	200	40	No
2	M	11/24/2007	53	2	0	3	2	2	2	1	1	1	1	N	H	N	2	2	3A	2	9.6	1	2	2	Y	Y	11/24/2007	03/01/2008	3	200	40	No
3	M	09/02/2008	57	2	0	3	2	2	2	1	1	1	1	N	H	NA	2	2	3A	2	6.2	1	1	3	Y	Y	09/14/2008	11/06/2009	14	200	20	No
4	F	06/29/2007	62	2	0	8	2	2	2	2	2	1	1	N	N	H	1	2	1A	2	0	7	2	3	Y	Y	07/03/2007	07/04/2008	12	200	20	y
5	M	02/05/2008	55	3,15	0	3	1	2	2	2	2	2	0	N	NA	H	1	3	2B	3	0	5	1	2	Y	N	02/05/2008	06/30/2009	17	200	40	No
6	M	04/08/2011	58	5	0	2	2	1	2	2	2	2	1	Y	H	H	2	3	3B	3	2.48	1	1	3	Y	Y	04/08/2011	08/16/2011	4	100	20	No
7	F	10/15/2010	32	1,2, 6	0	3	1	2	2	1	1	1	1	N	H	N	2	2	3A	2	6	2	1	2	Y	Y	10/20/2010	04/29/2011	6	150	40	No
8	M	04/17/2006	50	2	0	2	2	2	2	1	2	1	0	N	N	N	1	1	1A	1	4.6	1	1	1	Y	Y	05/29/2006	02/02/2007	8	200	40	No
9	M	07/01/2005	65	1,3,4	0	1.5	1	2	2	2	1	2	1	N	NA	H	2	3	3B	3	8	1	1	3	N	N	07/01/2005	11/01/2005	4	200	40	No
10.00	F	09/30/2009	57	6	0	3	2	2	2	1	2	1	1	N	NA	NA	2	1	3A	1	5.5	1	1	3	Y	Y	09/30/2009	03/26/2010	6	200	20	No
11	M	05/03/2010	55	10,11, 12	0	6	2	2	2	1	2	1	1	N	H	NA	2	2	2A	2	1.4	1	1	2	Y	Y	08/06/2010	02/01/2011	6	150	20	No
12	M	02/26/2008	35	2,5	0	15	1	2	2	1	1	1	1	N	N	H	2	3	2B	3	11.24	1	1	2	Y	Y	03/03/2008	05/09/2008	2	200	40	No
13	M	01/29/2008	56	2,7	0	6	2	2	2	1	2	1	1	N	H	N	2	1	2A	1	0.8	1	1	1	Y	Y	01/29/2008	07/29/2008	6	150	20	y
14	M	10/23/2010	56	7	0	0.5	2	2	2	1	2	1	1	N	NA	NA	1	1	1A	1	3.37	1	2	2	Y	Y	11/05/2010	05/27/2011	7	150	20	No
15	M	05/18/2007	63	2	0	4	1	2	2	1	1	1	1	N	N	H	2	3	3A	3	4.8	2	1	2	Y	Y	05/29/2007	10/17/2008	17	100	40	No
16	M	08/11/2007	47	1,3	0	1	1	1	2	1	1	2	1	N	N	H	1	3	3B	3	2.5	1	1	2	Y	Y	08/21/2007	06/16/2008	10	200	40	No
17	F	07/09/2010	48	2	0	2	2	2	2	1	2	1	1	N	N	H	2	2	1A	2	5.6	1	1	3	Y	Y	07/10/2010	10/15/2010	3	150	20	No
18	M	10/12/2009	78	2	0	8	2	2	2	1	2	1	1	N	H	NA	1	1	2A	1	2.3	1	1	3	Y	N	12/08/2009	09/10/2010	9	100	20	y
19	M	12/15/2005	57	5	0	1	1	2	2	1	1	1	1	N	N	N	1	1	2A	1	4.5	1	2	2	Y	N	01/13/2006	07/01/2006	6	100	40	No
20	M	11/20/2008	48	2	0	1	2	2	2	2	1	2	1	Y	N	NA	1	3	2B	3	6.19	1	1	2	Y	N	11/26/2008	01/23/2009	2	200	40	No
21	M	11/04/2008	56	2	0	18	1	2	2	1	1	1	1	N	NA	NA	1	2	3A	2	3.2	1	1	2	Y	Y	11/04/2008	02/02/2009	3	200	40	No
22	M	08/02/2008	51	2	0	3	1	2	2	1	2	2	1	N	N	H	1	3	2B	3	4.5	1	1	2	Y	Y	07/27/2008	08/27/2008	1	200	40	No
23	M	06/25/2011	58	2,7	0	3	2	2	2	1	2	1	1	Y	H	H	1	1	1A	1	3.35	1	3	3	Y	Y	06/27/2011	12/02/2011	5	200	40	No
24	M	02/16/2007	29	14	0	3	2	2	2	1	2	1	1	Y	NA	NA	2	2	2A	2	0	5	1	3	Y	N	02/16/2007	03/07/2008	13	100	40	No
25	M	02/01/2006	64	10	0	1	1	2	2	1	1	2	0	N	N	H	1	3	3B	3	3.3	1	1	2	Y	Y	02/20/2006	07/21/2006	5	200	40	No
26	F	09/01/2008	80	2	0	2	1	1	1	1	1	1	1	N	N	N	2	2	2A	2	3.5	1	2	1	Y	N	09/05/2008	11/04/2008	2	100	20	No
27	F	04/11/2006	56	1	0	6	1	1	2	2	1	1	0	N	N	NA	1	4	3A	4	5.2	1	1	3	Y	N	05/16/2006	05/28/2006	0	100	40	No
28	F	12/01/2006	51	1,2,3, 4	0	7	1	2	2	2	1	2	1	N	N	H	1	4	3B	4	4.8	1	1	1	Y	Y	12/07/2006	07/06/2007	7	200	40	y
29	M	09/22/2009	55	2	0	6	2	2	2	2	2	1	1	N	NA	N	2	3	3A	3	5.85	1	1	2	Y	Y	09/22/2009	09/17/2010	12	200	20	y
30	M	07/01/2005	49	2	0	2	2	2	2	1	1	1	1	N	N	H	2	3	1A	3	7.2	1	2	3	N	N	07/01/2005	01/24/2006	7	200	40	No
31	F	09/19/2006	56	2	0	2	2	2	2	1	1	1	0	Y	N	H	1	4	1A	4	2	1	3	3	N	N	10/01/2006	05/15/2007	8	100	40	y
32	M	09/16/2005	62	2,3,4, 7	0	3	1	2	2	2	1	2	1	Y	H	H	1	3	3B	3	6.65	1	1	3	Y	Y	09/16/2005	09/16/2006	12	100	40	No
33	M	05/11/2009	54	14	0	12	2	2	2	1	2	1	1	Y	NA	NA	2	4	2A	4	0.51	4	2	1	Y	N	05/19/2009	12/01/2009	7	100	20	No
34	M	07/02/2006	61	14	0	3	2	2	2	1	2	1	1	Y	N	H	1	4	2A	4	2	2	2	3	Y	Y	07/20/2006	01/31/2007	7	200	20	y
35	M	10/01/2006	58	2	0	2	1	2	2	2	1	2	1	N	N	H	1	3	3B	3	3.3	2	1	3	Y	N	10/01/2006	03/02/2007	5	200	20	No
36	F	02/25/2011	50	2	0	2	2	2	2	1	2	1	1	Y	N	NA	1	1	2A	1	2	1	2	1	Y	Y	03/04/2011	09/30/2011	7	150	20	No
37	M	06/24/2005	53	1,2,3	0	5	1	2	2	1	2	2	1	N	NA	H	1	3	3B	3	0	5	1	2	N	Y	07/09/2005	04/01/2006	9	200	40	No
38	M	11/18/2008	68	14	0	4	1	2	2	1	1	1	1	Y	N	N	1	3	2A	3	4.93	2	1	2	Y	Y	11/23/2008	02/24/2009	3	150	40	No
39	M	08/21/2008	59	14	0	1	1	2	2	1	1	2	1	Y	NA	H	1	3	2B	3	4.5	1	1	2	Y	N	08/30/2008	10/26/2008	2	150	20	No
40	M	11/21/2008	37	2,8	0	5	1	2	2	2	2	2	1	N	H	H	2	3	3B	3	BICLONAL	6	2	2	Y	N	11/25/2008	01/06/2009	1	200	20	y
41	M	11/10/2005	56	1,2,3	0	3	1	2	2	1	2	2	1	Y	N	H	1	3	3A	3	1.63	1	1	2	Y	N	02/17/2006	10/24/2006	8	200	40	No
42	M	05/10/2011	41	2	0	1	2	1	2	1	2	1	1	N	NA	H	2	3	2A	3	5	2	1	3	Y	Y	05/10/2011	12/06/2011	7	100	40	No
43	F	09/11/2006	48	2	0	2	1	2	2	2	1	1	1	N	N	H	2	2	2A	2	5.75	2	2	2	Y	Y	09/20/2006	04/24/2007	7	200	40	No
44	M	03/17/2009	52	2	2	13	2	2	2	1	2	1	0	N	N	NA	1	1	1A	1	3.06	1	3	3	Y	N	03/17/2009	08/06/2010	17	100	20	No
45	M	12/15/2009	52	9	0	3	2	2	2	1	1	1	1	N	N	NA	1	2	3A	2	6.6	1	1	2	Y	Y	12/15/2009	06/04/2010	6	100	20	No
46	M	01/17/2008	46	2,3	0	1	2	2	2	2	2	2	1	N	H	NA	1	3	2B	3	0	5	1	2	Y	Y	02/02/2008	05/30/2008	4	100	40	No
47	M	08/14/2009	52	2	0	1	1	2	2	2	1	1	1	N	N	NA	2	3	3A	3	5.7	2	1	1	Y	N	08/18/2009	02/18/2010	6	150	20	No

48	M	09/24/2008	53	1,3	0	2	1	2	2	1	2	2	0	N	N	N	1	3	3B	3	1.6	1	1	2	Y	N	09/25/2008	11/04/2008	1	200	20	No
49	M	06/25/2006	54	16	0	1	1	2	2	2	1	1	0	N	NA	NA	1	4	2A	4	3.5	1	2	1	S	Y	04/10/2007	08/03/2007	4	100	40	No
50	M	01/18/2010	49	2	0	0.5	2	2	2	1	2	1	1	N	N	N	1	1	1A	1	3.3	1	2	3	Y	N	01/20/2010	04/20/2010	3	200	20	No
51	M	12/08/2008	68	14	0	2	2	2	2	1	2	1	1	Y	H	N	1	4	2A	4	1.5	1	2	3	Y	N	12/08/2008	06/19/2009	6	200	20	No
52	F	03/04/2008	55	1	0	7	2	2	2	1	2	1	1	N	H	N	1	3	1A	3	1.99	1	2	2	Y	Y	03/07/2008	09/12/2008	6	100	40	y
53	M	05/23/2008	65	2	0	1	1	2	2	1	1	1	1	N	N	N	2	2	3A	2	7.21	1	1	3	Y	Y	05/27/2008	09/12/2008	4	100	40	y
54	F	09/14/2007	52	1,2	0	5	2	2	2	1	2	1	1	N	N	NA	1	1	1A	1	2.7	1	2	1	Y	Y	09/18/2007	01/15/2008	4	200	40	No
55	F	06/23/2005	62	1,2,3	0	12	1	2	2	1	2	2	1	N	N	H	1	3	3B	3	FAINT	5	1	2	Y	N	06/28/2005	01/12/2007	19	100	40	No
56	M	01/30/2006	59	1,5	0	2	1	2	2	1	2	2	0	N	N	H	2	3	2B	3	3.1	1	1	2	Y	N	02/10/2006	06/26/2006	5	150	40	No
57	M	02/23/2008	56	2	0	2	2	2	2	1	2	1	1	N	N	N	1	1	2A	1	0	5	2	1	Y	Y	03/02/2008	09/02/2008	6	200	20	No
58	M	08/07/2005	39	9	0	1	2	2	2	1	2	1	1	Y	NA	NA	1	4	2A	4	0	5	3	3	Y	Y	08/07/2009	05/03/2010	9	200	40	No
59	M	07/01/2009	54	14	0	1	2	2	2	1	2	1	1	Y	NA	NA	1	4	2A	4	0	5	1	3	Y	Y	07/17/2009	03/23/2010	8	100	20	No
60	F	02/05/2007	52	1,3	0	3	1	2	2	1	1	2	1	N	N	N	1	3	3B	3	0	5	1	3	Y	N	02/15/2007	10/15/2007	8	200	40	No
61	M	06/15/2011	62	2	0	2	2	2	2	1	2	1	1	N	N	N	1	4	3A	4	0	5	2	3	Y	Y	07/22/2011	11/18/2011	4	200	20	No
62	M	02/19/2007	61	2	0	4	1	2	2	1	1	1	1	N	N	N	1	2	2A	2	5.6	1	1	2	Y	N	02/20/2007	08/20/2007	6	150	40	No
63	F	10/04/2005	55	1	0	6	1	2	2	2	2	2	1	N	N	NA	1	3	3B	3	0.8	5	1	2	Y	Y	10/11/2005	03/28/2006	6	200	40	No
64	M	01/07/2010	59	6,14	0	2	2	2	2	1	2	1	1	Y	H	NA	1	4	2A	4	0	5	3	3	Y	Y	01/19/2010	09/18/2010	8	150	40	y
65	F	08/09/2006	57	2,9	0	6	1	2	2	2	2	1	1	N	N	H	1	1	2A	1	3.2	1	2	3	Y	Y	08/20/2006	12/07/2007	16	100	20	No
66	M	05/31/2005	21	7	0	1.5	2	2	2	1	1	1	1	Y	N	H	1	4	2A	4	3.75	4	2	3	N	Y	07/10/2005	01/17/2006	6	200	40	No
67	M	07/28/2010	57	8,	0	6	2	2	2	1	2	1	1	N	N	N	1	1	2A	1	2.8	2	1	3	Y	Y	07/28/2010	05/10/2011	10	200	20	No
68	M	09/14/2007	50	2,10	0	4	2	2	2	1	2	1	1	N	NA	NA	1	1	1A	1	2.4	4	2	2	Y	Y	09/14/2007	12/21/2007	3	100	40	No
69	M	04/26/2008	47	2	0	2	1	2	2	1	1	1	1	N	N	H	1	3	3A	3	8	1	2	3	Y	Y	05/10/2008	12/02/2009	19	100	40	No
70	F	07/07/2009	42	1,2	0	4	2	2	2	1	2	1	1	Y	NA	N	1	1	3A	1	FAINT	1	2	2	Y	Y	07/07/2009	10/15/2010	16	100	20	y
71	F	08/05/2011	43	2,9	0	3	1	2	2	2	1	2	1	N	N	H	1	3	3B	3	BICLONAL	6	1	2	Y	Y	08/20/2011	12/23/2011	4	200	40	y
72	M	01/20/2006	61	14	0	8	2	2	2	1	2	1	1	Y	N	NA	1	2	2A	2	2.4	2	1	2	Y	Y	01/20/2006	05/20/2007	16	100	40	No
73	M	08/26/2008	66	1,2	0	12	1	2	2	1	1	1	0	N	N	NA	1	1	2A	2	2	4	2	3	Y	Y	08/26/2008	07/28/2009	11	100	20	No
74	F	02/03/2009	32	1,2	0	2	1	2	2	1	1	1	1	N	N	H	1	1	3A	2	8.4	1	2	2	Y	Y	02/06/2009	08/21/2009	7	150	20	No
75	F	07/30/2004	50	1,8	0	4	1	2	2	1	2	1	1	N	NA	NA	2	3	3A	3	3.5	1	1	3	Y	Y	07/30/2004	06/28/2005	11	200	40	No
76	M	07/27/2007	62	1	0	2	1	2	2	1	2	1	1	N	N	H	2	2	2A	2	0	5	2	2	Y	Y	08/03/2007	05/26/2009	22	200	40	y
77	M	11/16/2010	69	3	0	1	1	2	2	1	1	2	1	N	NA	NA	1	3	2B	3	BICLONAL	6	1	2	Y	Y	11/16/2010	03/29/2011	4	100	40	No
78	M	02/17/2006	54	5	0	12	1	2	2	1	1	1	0	N	H	H	1	4	2A	4	4.5	1	1	1	Y	N	03/03/2006	08/31/2006	6	200	40	No
79	M	04/06/2011	58	9	0	6	2	2	2	2	1	1	1	Y	NA	NA	1	1	1A	2	4	1	1	3	Y	Y	05/07/2011	12/07/2011	7	100	20	No
80	F	11/03/2009	65	2	0	1	2	2	2	1	2	1	1	N	H	N	1	1	1A	1	3.1	1	2	1	Y	Y	11/03/2009	04/30/2010	6	200	20	No
81	M	11/02/2007	61	2	0	3	2	2	2	1	2	1	1	N	H	H	1	1	2A	1	1.8	1	2	2	Y	N	11/13/2007	07/22/2008	8	150	40	y
82	F	09/07/2010	45	12	0	3	1	1	1	1	1	1	1	N	N	N	2	4	3A	4	5.49	1	1	3	Y	N	09/07/2010	03/01/2011	6	100	20	No
83	M	07/12/2007	66	1	0	3	2	1	1	1	1	1	0	N	N	NA	1	2	1A	2	3.4	2	1	2	Y	Y	07/17/2007	09/12/2008	14	100	40	No
84	M	05/27/2011	54	2	0	2	2	2	2	1	2	1	1	Y	H	N	1	1	3A	1	0.6	1	2	3	Y	Y	04/18/2011	09/06/2011	5	200	40	No
85	M	08/17/2006	55	1,2	0	6	1	2	2	1	2	2	1	Y	NA	N	1	3	3B	3	0	5	2	2	y	Y	08/22/2006	12/08/2006	4	100	40	y
86	F	03/02/2004	53	2	0	2	2	2	2	1	2	1	1	N	NA	N	1	2	2A	2	1.3	1	2	3	N	Y	03/05/2004	10/05/2004	7	200	40	No
87	M	10/10/2006	44	14	1	25	2	2	2	1	2	1	1	Y	N	NA	1	1	2A	1	3.1	4	2	3	Y	Y	10/13/2006	08/21/2007	10	200	40	y
88	M	08/11/2009	67	1,5	0	18	1	2	2	1	1	1	0	N	H	N	1	2	3A	2	3.21	1	1	3	Y	Y	09/04/2009	07/21/2010	11	150	20	y
89	F	01/12/2007	57	1	0	3	1	2	2	1	1	1	1	N	N	N	1	3	3A	3	6.5	2	1	2	Y	Y	08/18/2006	03/02/2007	7	200	40	y
90	M	11/28/2008	52	2, 14	0	0.5	2	2	2	1	2	1	1	Y	H	N	1	2	2A	2	1.5	2	2	2	Y	Y	12/01/2008	05/23/2009	6	200	20	No
91	M	07/11/2005	66	1	0	6	1	2	2	1	1	1	0	N	N	H	1	3	3A	3	6.3	1	1	3	N	N	07/11/2005	02/11/2006	7	200	40	No
92	F	01/17/2006	64	1,2	0	2	1	2	2	1	2	1	1	N	N	N	1	4	3A	4	0.95	4	1	3	Y	N	02/17/2006	11/10/2006	9	100	40	No
93	F	11/11/2009	64	1,5	0	3	1	2	2	1	2	1	1	N	N	N	1	1	3A	1	6	1	1	3	Y	Y	11/11/2009	12/14/2010	13	200	20	No
94	M	10/10/2007	54	2,8	0	6	1	2	2	2	1	1	1	N	N	H	1	3	3A	3	4.16	1	1	3	Y	Y	10/10/2007	11/14/2008	13	200	20	y
95	M	08/20/2005	54	2,3,4	0	2	1	2	2	2	2	2	1	N	N	H	2	3	3B	3	0	5	3	2	N	Y	09/14/2005	02/03/2006	5	100	16	No

96	M	03/01/2010	38	2	0	36	2	2	2	1	2	1	1	N	N	NA	1	4	3A	4	0	5	2	2	Y	Y	03/16/2010	03/15/2011	12	100	20	No
97	M	04/28/2007	41	1,2	0	18	1	2	2	2	1	1	1	N	N	N	1	3	3A	3	9.5	1	1	3	Y	Y	06/22/2007	01/04/2008	7	200	40	No
98	F	02/18/2010	50	2, 7	0	1	2	2	2	1	2	1	1	Y	N	N	1	1	1A	1	FAINT	5	1	3	Y	Y	03/09/2010	12/16/2010	9	200	20	No
99	F	12/12/2008	55	2	0	3	1	2	2	2	1	2	1	N	N	NA	1	3	3B	3	3.5	6	1	2	Y	Y	12/12/2008	03/13/2009	3	200	20	y
100	M	11/12/2010	59	2	0	4	1	2	2	1	1	2	1	N	N	H	1	4	3B	4	4.7	1	1	3	Y	Y	11/12/2010	08/19/2011	9	100	20	No
101	M	06/07/2010	49	2	0	3	2	2	2	1	1	1	1	N	N	H	1	2	3A	2	6	1	1	3	Y	Y	06/08/2010	12/08/2010	6	200	20	No
102	F	06/25/2008	61	1	0	12	1	2	2	1	2	1	0	N	N	N	1	3	2A	3	BICLONAL	6	2	1	Y	Y	06/25/2008	07/15/2009	13	200	20	y
103	F	11/18/2006	38	2	0	0.5	1	2	2	2	1	2	0	N	N	H	2	3	3B	3	11.2	1	1	2	Y	Y	11/28/2006	09/28/2007	10	200	40	No
104	M	09/08/2008	42	2,8,14	0	6	2	2	2	1	2	1	1	N	N	N	1	1	1A	1	1.3	1	2	3	Y	Y	09/26/2008	04/03/2009	6	200	20	No
105	M	01/23/2007	65	2	0	1	2	2	2	1	2	1	1	N	N	NA	1	1	2A	1	0.3	2	3	3	Y	Y	02/13/2007	11/13/2007	9	200	40	No
106	M	09/29/2009	54	2	0	6	2	2	2	1	1	1	1	N	N	N	1	2	3A	2	3.2	2	2	1	Y	Y	09/29/2009	02/05/2010	4	100	20	No
107	M	11/13/2007	53	2	0	6	1	2	2	1	2	1	1	Y	NA	N	2	2	3A	2	2	2	2	1	Y	Y	11/13/2007	07/20/2008	8	100	40	No
108	M	08/04/2005	68	1	0	4	1	2	2	2	1	1	0	N	NA	H	2	3	3A	3	6.5	1	1	3	Y	Y	08/23/2005	07/31/2007	24	200	40	y
109	M	08/28/2007	52	1,2	0	3	1	2	2	1	1	1	1	N	N	H	1	2	2A	2	4	1	2	3	Y	Y	08/31/2007	03/11/2008	6	100	40	No
110	M	10/10/2007	31	2	0	2	1	2	2	1	2	1	1	N	H	NA	2	2	3A	2	5.6	4	1	2	Y	Y	10/10/2007	04/20/2008	6	200	40	No
111	M	12/18/2008	60	1,2,3	0	3	1	2	2	2	1	2	1	N	NA	N	1	3	3B	3	9.5	1	3	3	Y	N	12/22/2008	06/26/2009	6	200	40	No
112	M	01/11/2011	65	2	0	2	1	2	2	1	1	1	1	Y	NA	N	1	1	2A	2	3.8	1	2	3	Y	Y	01/18/2011	07/15/2011	6	150	20	y
113	F	06/10/2008	60	2	0	3	1	2	2	1	2	1	1	N	NA	H	1	3	3A	3	2.5	1	1	2	Y	Y	06/15/2008	02/13/2009	8	200	20	y
114	M	03/25/2011	50	1,2	0	4	1	2	2	1	2	1	1	N	N	N	1	2	3A	2	2	5	1	1	Y	Y	03/28/2011	09/30/2011	6	150	20	No
115	M	04/25/2008	73	1,3	0	1	1	2	2	1	1	2	0	N	N	N	1	4	3B	4	5.3	1	1	2	Y	N	04/29/2008	03/10/2009	11	150	20	No
116	F	02/08/2006	47	1	0	2	1	2	2	1	1	1	0	N	N	NA	2	2	3A	2	7.7	1	1	3	N	Y	02/08/2006	08/11/2006	6	200	40	No
117	M	11/07/2006	42	11	0	12	1	2	2	1	1	1	0	N	N	N	1	1	2A	2	4	1	2	3	Y	N	12/19/2006	07/29/2008	20	100	40	No
118	M	07/09/2009	48	14	0	4	1	2	2	1	2	1	1	Y	N	N	1	2	3A	2	3.6	2	2	2	Y	Y	08/11/2009	02/17/2010	6	100	20	No
119	M	08/24/2008	49	2	0	3	2	2	2	1	2	1	1	N	H	N	1	1	2A	1	Dec gam	5	2	1	Y	Y	08/24/2008	04/08/2009	8	200	20	No
120	M	01/25/2011	47	14	0	12	1	2	2	1	1	1	1	Y	NA	NA	1	1	2A	2	8.3	4	2	1	Y	Y	01/25/2011	09/13/2011	8	100	40	No
121	M	12/18/2007	41	1,2	0	0.5	1	2	2	1	1	1	1	N	H	NA	1	2	2A	2	1.6	1	2	2	Y	Y	12/25/2007	10/21/2008	10	200	40	No
122	M	09/08/2009	53	1,8	0	9	1	1	2	1	2	2	1	N	H	H	2	3	3B	3	2.3	1	3	2	Y	N	09/18/2009	12/11/2009	3	100	20	No
123	M	04/04/2008	58	2,14	0	6	2	2	2	1	1	1	1	Y	N	N	1	1	1A	2	7	1	3	2	Y	Y	04/04/2008	01/30/2009	10	150	20	No
124	F	03/18/2011	50	2,7	0	2	2	2	2	1	2	1	1	Y	NA	NA	2	1	1A	1	Dec gam	5	1	3	Y	Y	03/18/2011	09/23/2011	6	100	40	No
125	M	11/22/2005	69	1, 9	0	3	1	1	1	1	1	1	1	N	NA	NA	1	2	3A	2	BROAD	3	1	2	N	Y	11/30/2005	03/30/2007	16	200	20	y
126	M	02/17/2006	54	1	0	2	1	2	2	1	1	1	1	N	N	NA	1	1	3A	2	8.5	1	3	3	Y	Y	02/17/2006	LTF	LTF	200	40	LTF
127	M	11/23/2007	61	2	0	12	1	2	2	1	2	1	1	N	H	N	1	1	3A	1	3.2	1	2	1	Y	Y	11/30/2007	LTF	LTF	100	40	LTF
128	M	12/08/2011	53	2,8	0	12	1	2	2	1	2	1	0	N	NA	N	1	2	3A	2	4.6	2	1	3	Y	Y	12/16/2011	LTF	LTF	200	20	LTF
129	M	04/05/2011	60	6	0	1	1	2	2	1	1	1	1	N	NA	NA	1	3	3A	3	4	1	1	2	Y	Y	04/06/2011	LTF	LTF	100	20	LTF
130	F	07/01/2011	43	3,5	0	3	1	2	2	1	1	2	0	N	N	N	1	3	3B	3	6	1	1	2	Y	N	07/01/2011	08/02/2011	LTF	200	40	LTF
131	M	02/20/2007	57	2	0	3	1	2	2	1	1	1	1	N	H	N	1	2	3A	2	6.9	1	2	2	Y	Y	02/20/2007	04/17/2007	LTF	100	40	LTF
132	F	03/01/2011	48	1,3,4, 6,15	0	3	1	2	2	1	2	2	1	N	NA	NA	1	3	2B	3	0	5	1	2	Y	N	06/03/2011	09/03/2011	LTF	100	20	LTF
133	M	04/18/2005	51	2,3,4	0	1	1	2	2	2	1	2	1	N	N	H	1	3	3A	3	5.6	4	1	2	N	N	04/27/2005	LTF	LTF	100	8	LTF
134	M	12/09/2008	45	2	0	12	1	2	2	1	2	1	1	N	H	H	1	3	2A	3	0	5	1	2	Y	Y	12/12/2008	LTF	LTF	200	20	LTF
135	F	09/30/2011	72	2	0	12	2	2	2	1	2	1	1	N	N	N	1	1	1A	1	1.2	3	2	1	Y	Y	10/07/2011	LTF	LTF	100	20	LTF
136	F	07/12/2005	36	14	0	24	2	2	2	1	2	1	1	Y	N	N	1	2	2A	2	0	7	2	3	N	Y	07/12/2005	10/22/2005	LTF	200	40	LTF
137	F	11/28/2011	55	14	0	3	2	2	2	1	2	1	1	Y	H	N	1	3	3A	3	0.6	5	1	2	Y	Y	12/27/2011	LTF	LTF	100	20	LTF
138	M	11/23/2007	52	2,8	0	12	1	2	2	1	1	1	1	N	N	H	2	3	3A	3	FAINT	2	1	2	Y	Y	12/04/2007	LTF	LTF	50	40	LTF
139	M	06/30/2007	43	1,3,4	0	1	1	2	2	2	1	2	1	N	NA	H	2	3	3B	3	5.1	1	1	2	Y	N	06/30/2007	LTF	LTF	100	40	LTF
140	F	02/01/2009	58	1,5,8	0	12	1	2	2	1	1	2	1	N	H	H	2	3	3B	3	5	6	1	2	Y	N	02/03/2009	LTF	LTF	100	20	LTF
141	M	10/15/2010	45	1,2,3	0	7	1	2	2	1	2	2	1	N	N	H	2	3	3B	3	1	5	1	2	Y	N	02/12/2010	LTF	LTF	50	20	LTF
142	M	06/26/2007	72	1	0	9	2	2	2	1	1	1	1	N	N	N	2	3	3A	3	3.2	2	1	3	Y	N	06/27/2007	LTF	LTF	100	40	LTF
143	M	07/15/2008	48	1,2	0	8	1	2	2	1	1	1	1	N	N	NA	1	2	3A	2	4.5	2	1	2	Y	N	07/18/2008	08/18/2008	1	200	40	No

144	M	11/30/2007	55	2	0	2	2	2	2	1	2	1	1	N	NA	NA	1	4	2A	4	1	4	2	1	Y	Y	12/21/2007	02/29/2008	2	200	40	No
145	F	06/24/2011	53	2	0	5	1	2	2	2	2	1	1	N	NA	N	1	1	3A	1	Dec gam	5	2	1	Y	Y	06/24/2011	09/27/2011	3	100	40	No
146	F	08/11/2009	58	1,2,7	0	2	2	2	2	1	2	1	1	N	N	H	1	2	3A	2	0	5	1	2	Y	Y	08/11/2009	12/22/2009	4	200	20	No
147	F	11/13/2009	45	1	0	3	2	1	1	1	2	1	0	N	H	NA	2	1	3A	1	FAINT	5	1	3	Y	Y	11/27/2009	08/17/2010	9	150	20	No
148	F	07/24/2007	50	2	0	2	1	2	2	1	1	1	1	N	N	N	1	2	3A	2	7.2	1	1	3	Y	Y	07/24/2007	02/12/2008	7	200	40	No
149	M	02/14/2007	76	2,8	0	12	1	2	2	1	1	1	0	N	N	H	1	3	3A	3	1.54	1	2	2	C	N	03/01/2007	10/31/2007	8	100	40	No
150	F	07/31/2007	46	2	0	2	2	2	2	2	2	1	1	N	NA	H	1	2	2A	2	0.9	5	1	3	Y	Y	07/31/2007	10/23/2007	3	200	40	No
151	M	03/08/2011	56	2	0	2	1	2	2	1	1	1	1	N	N	NA	1	1	3A	2	BICLONAL	2	1	2	Y	Y	03/11/2011	09/05/2011	6	100	40	No
152	F	06/03/2011	45	2,8	0	3	2	2	2	2	1	1	1	N	N	N	1	3	2A	3	5.2	1	1	3	y	Y	06/10/2011	07/12/2011	1	100	40	No
153	M	12/04/2009	66	1	0	6	1	2	2	1	1	1	0	N	NA	NA	2	3	3A	3	BICLONAL	6	1	3	Y	Y	12/04/2009	09/03/2010	9	100	20	No
154	M	04/26/2011	53	2	0	2	2	2	2	1	2	1	1	Y	H	N	1	1	2A	1	1.12	1	1	3	Y	Y	04/26/2011	11/04/2011	6	100	20	No
155	F	01/31/2006	43	2	0	6	1	2	2	2	2	2	1	N	N	H	1	3	3B	3	3.4	2	1	2	Y	N	01/31/2006	11/17/2006	10	200	20	No
156	M	01/10/2010	55	2	0	6	2	2	2	1	2	2	1	N	N	H	2	4	2B	4	0	5	1	3	Y	N	01/14/2010	09/07/2010	8	150	40	No
157	M	05/02/2004	70	2	0	1	2	2	2	2	1	2	1	N	NA	NA	1	3	2B	3	3.2	1	1	3	N	N	06/18/2004	02/14/2006	20	200	40	No
158	M	08/25/2004	40	2, 9	0	2	1	2	2	1	1	1	1	Y	N	N	1	1	3A	2	5.3	1	1	3	N	Y	09/28/2004	03/21/2005	6	400	40	No
159	M	08/03/2006	59	12	0	24	2	2	2	1	1	1	1	N	N	N	1	1	2A	2	5	1	1	3	Y	Y	08/18/2006	02/23/2007	6	100	40	y
160	M	09/05/2006	54	2,8,14	0	1.5	2	2	2	2	1	1	1	Y	N	N	1	1	3A	2	4.4	1	1	3	Y	Y	09/06/2006	07/03/2007	10	200	40	No
161	F	03/09/2004	40	2,13	0	2	1	1	1	2	1	1	0	N	NA	NA	1	4	2A	4	4.5	1	1	3	N	Y	03/09/2004	07/12/2004	4	200	40	No
162	F	09/13/2011	60	11	0	0.5	1	2	2	1	2	1	1	Y	N	N	1	2	2A	1	3	1	2	1	Y	Y	09/30/2011	12/27/2011	3	100	40	No
163	M	04/19/2010	52	2	0	2	2	2	2	1	1	1	1	N	N	N	1	1	1A	2	1.59	1	2	2	Y	Y	04/25/2010	12/10/2010	8	150	20	No
164	M	12/05/2006	71	1	0	12	1	2	2	1	2	1	1	N	H	NA	1	3	3A	3	2.55	1	2	1	Y	N	03/02/2007	09/08/2007	6	100	40	No
165	M	03/24/2006	53	1	0	48	1	2	2	1	1	1	0	N	N	N	1	2	2A	2	1.16	5	1	2	Y	N	04/07/2006	10/27/2006	7	200	40	No
166	F	05/31/2006	56	14	0	3	2	2	2	1	2	1	1	Y	NA	NA	1	2	1A	2	1.4	2	2	3	Y	Y	06/02/2006	11/28/2006	6	200	40	No
167	M	05/20/2005	51	14	1	6	1	2	2	1	2	1	1	Y	NA	NA	1	1	2A	1	0	7	2	3	N	Y	06/03/2005	12/03/2005	6	200	40	No
168	F	01/22/2010	42	1,13	0	3	1	2	2	1	2	1	0	N	H	N	2	4	2A	4	8.1	1	2	2	Y	N	01/22/2010	08/21/2010	7	100	20	No
169	M	11/14/2008	63	1,2,6,10	0	18	1	2	2	1	2	1	1	N	NA	N	1	3	3A	3	0.25	1	2	3	Y	Y	11/18/2008	01/08/2010	14	200	20	No
170	M	10/13/2008	54	2	0	2	1	2	2	1	2	1	1	N	N	NA	1	1	2A	1	4.9	3	1	1	Y	Y	10/25/2008	05/01/2009	6	200	20	y
171	M	12/03/2010	31	2	0	6	2	2	2	1	2	1	1	N	N	N	1	1	2A	1	0	5	1	2	Y	Y	12/09/2010	08/22/2011	9	200	40	No
172	M	03/21/2011	31	2	0	3	1	2	2	1	1	1	1	N	NA	N	1	4	3A	4	7.42	1	1	3	Y	Y	03/30/2011	10/11/2011	7	200	40	No
173	M	01/11/2011	63	1	0	6	1	1	2	1	2	1	0	N	H	NA	2	3	3A	3	0	5	1	2	Y	N	01/14/2011	08/02/2011	7	150	40	y
174	M	12/18/2006	50	2	0	6	1	2	2	1	2	1	1	N	NA	NA	1	1	2A	1	4.8	1	1	3	Y	Y	01/09/2007	02/01/2008	13	100	40	No
175	M	05/03/2008	51	7,12,14	0	18	2	2	2	1	2	1	1	Y	N	N	1	1	2A	1	4.5	1	2	1	Y	N	05/10/2008	12/23/2008	8	100	40	No
176	F	06/21/2011	50	1,5	0	6	1	2	2	1	2	1	0	N	N	NA	1	3	3A	3	FAINT	1	1	2	Y	N	06/21/2011	10/30/2011	4	100	40	No
177	F	11/04/2008	68	1,2	0	12	1	2	2	1	1	1	1	N	N	N	1	3	3A	3	9.7	3	1	2	Y	N	11/04/2008	08/31/2010	22	100	20	y
178	M	05/02/2008	43	2	0	6	2	2	2	1	2	1	1	N	N	N	1	1	1A	1	FAINT	5	1	2	Y	Y	05/02/2008	11/12/2008	6	100	20	No
179	M	02/10/2006	45	2,7	0	6	1	2	2	1	2	1	1	Y	NA	NA	1	4	2A	4	0.3	5	1	2	N	Y	02/14/2006	10/20/2006	8	200	40	y
180	M	11/24/2009	61	3	0	0.5	1	2	2	1	2	2	0	N	N	H	1	3	2B	3	2.26	1	1	2	Y	N	11/24/2009	11/26/2011	24	100	20	y
181	F	05/14/2010	49	2	0	2	1	2	2	1	3	1	1	Y	N	H	2	3	3A	3	6.6	2	1	3	Y	Y	05/14/2010	12/28/2010	8	100	20	No
182	M	10/02/2007	67	1,3	0	2	1	2	2	2	1	2	1	N	NA	H	2	3	3B	3	5.55	4	1	2	Y	N	10/09/2007	04/22/2008	7	200	40	y
183	M	03/23/2006	42	13	0	2.5	1	2	2	1	1	1	0	N	N	N	2	3	2A	3	10	1	2	3	Y	N	03/31/2006	11/14/2006	8	200	20	No
184	M	09/22/2007	29	2	0	1	2	2	2	2	1	1	1	Y	N	NA	1	1	3A	2	6	1	1	2	Y	Y	09/25/2007	04/01/2008	6	200	40	No
185	M	06/17/2008	40	7	0	3	2	2	2	1	2	1	1	Y	H	N	1	1	2A	1	2	1	2	1	Y	Y	06/24/2008	05/11/2009	11	200	40	No
186	M	05/09/2008	43	2,9	0	5	2	2	2	1	1	1	1	N	H	NA	1	1	2A	2	5	1	1	3	Y	Y	05/09/2008	08/08/2008	3	200	40	No
187	M	09/21/2007	49	1,2	0	4	1	2	2	1	2	2	1	N	H	N	2	4	3B	4	0.6	1	3	2	Y	Y	09/21/2007	06/12/2009	21	100	40	No
188	F	11/28/2006	53	2	0	6	1	1	1	1	1	1	1	Y	N	NA	1	3	3A	3	4.4	1	1	3	Y	Y	12/01/2006	05/01/2008	17	200	40	y
189	F	06/08/2007	55	7,14	1	48	2	2	2	1	2	1	1	Y	N	N	1	1	1A	1	0.77	4	2	3	Y	N	06/08/2007	05/09/2008	11	100	20	y
190	M	09/11/2007	33	1,5	0	1.5	1	1	1	1	2	1	0	N	NA	NA	1	1	3A	1	3	1	2	3	Y	Y	09/18/2007	03/25/2008	6	200	40	No
191	M	04/14/2009	47	1	0	2	1	2	2	1	2	2	1	N	N	N	2	2	3B	2	6.85	1	1	2	Y	Y	04/17/2009	04/22/2010	12	200	40	y

192	F	03/21/2005	38	2,7	0	9	1	2	2	1	1	1	1	Y	N	N	1	1	3A	2	3.4	1	2	2	N	Y	04/02/2005	11/01/2005	7	200	40	No
193	M	04/04/2010	43	2	0	2	1	2	2	1	1	1	1	N	N	N	2	3	3A	3	9.4	1	1	3	Y	N	04/20/2010	02/11/2011	10	100	40	No
194	F	07/26/2006	49	2	0	2	1	2	2	1	1	1	1	N	N	NA	1	1	2A	2	0.4	2	2	1	N	Y	07/31/2006	12/31/2006	5	200	40	No
195	M	01/19/2010	52	2	0	0.5	2	2	2	1	2	1	1	N	N	NA	1	1	2A	1	1.5	1	2	3	Y	Y	01/19/2010	01/11/2011	12	150	20	No
196	M	05/25/2010	57	14	0	0.5	2	2	2	1	1	1	1	Y	NA	NA	1	1	2A	1	3.2	1	2	3	Y	Y	06/15/2010	12/10/2010	6	100	20	No
197	M	08/10/2006	62	1,2	0	8	1	2	2	2	1	2	0	N	NA	H	1	4	3B	4	FAINT	5	1	2	Y	Y	08/22/2006	06/22/2007	10	200	20	No
198	M	12/23/2005	56	2	0	2	1	2	2	2	1	1	1	N	N	N	1	2	3A	2	5.1	2	2	2	Y	N	01/02/2006	10/28/2006	10	200	40	No
199	M	04/16/2004	72	1	0	4	1	2	2	1	1	1	0	N	N	N	2	4	3A	4	.5	1	1	3	N	Y	04/16/2004	09/06/2005	17	400	40	No
200	M	10/06/2006	65	2,14	1	180	2	2	2	1	2	1	1	Y	NA	NA	1	2	3A	2	3.2	1	2	3	Y	Y	10/10/2006	05/04/2007	7	200	40	y
201	M	06/23/2008	50	7,14	0	1	2	2	2	1	2	1	1	Y	N	NA	1	1	1A	1	3.67	4	2	3	Y	Y	06/23/2008	05/30/2009	11	150	20	y
202	F	12/23/2008	47	2	0	3	2	2	2	1	2	1	1	N	N	NA	1	1	1A	1	1.9	1	2	1	Y	Y	01/08/2009	03/19/2010	15	100	20	No
203	M	06/26/2006	64	2,3	0	6	1	2	2	2	2	2	1	N	N	H	1	4	3B	4	0.49	5	1	2	Y	N	07/04/2006	12/31/2006	6	200	40	No
204	F	02/16/2007	68	2,14	0	3	2	2	2	1	2	1	1	Y	N	NA	1	3	2A	3	3.9	2	1	2	Y	Y	02/16/2007	09/18/2007	7	200	40	No
205	M	05/09/2006	62	2,7	0	7	2	2	2	1	2	1	1	N	NA	N	1	4	2A	4	BICLONAL	6	2	3	Y	N	06/02/2006	12/02/2006	6	200	40	No
206	M	07/20/2007	52	2,7, 9	0	6	2	2	2	1	1	1	1	N	NA	NA	1	1	2A	2	4.58	1	1	1	Y	Y	07/20/2007	01/20/2008	6	100	40	No
207	F	09/11/2007	60	1,2	0	12	1	1	2	1	1	1	1	N	NA	NA	2	3	3A	3	5.2	1	1	3	N	Y	09/14/2007	09/12/2008	12	100	40	y
208	M	02/06/2009	48	9	0	1	2	2	2	1	2	1	1	N	N	H	2	1	2A	1	3.8	1	2	3	Y	Y	02/10/2009	09/07/2010	19	150	20	No
209	M	06/20/2008	49	1,2,13	0	8	1	1	2	1	1	1	1	N	N	H	2	1	3A	2	8.5	1	2	1	Y	Y	06/24/2008	04/03/2009	9	200	20	No
210	F	01/19/2007	62	1,2	0	4	1	2	2	1	1	1	1	Y	N	N	1	3	3A	3	4	1	2	1	Y	Y	01/31/2007	01/29/2008	12	100	40	y
211	M	07/10/2007	45	9	1	96	1	2	2	1	1	1	1	Y	N	N	1	2	3A	2	5	1	1	1	Y	Y	07/18/2007	08/22/2008	13	200	40	No
212	M	06/09/2006	64	2	0	18	2	1	2	1	2	2	1	N	N	N	1	3	2B	3	0	5	1	2	Y	Y	06/30/2006	08/07/2007	13	200	20	y
213	M	12/05/2008	54	2	0	36	2	2	2	1	2	1	1	N	N	N	1	1	1A	1	3.1	1	2	1	Y	Y	12/05/2008	12/05/2009	12	100	40	No
214	M	05/01/2007	56	9	0	1	1	2	2	1	1	1	1	N	N	NA	1	1	3A	2	4.83	4	1	2	Y	Y	05/02/2007	07/29/2008	15	150	8	No
215	F	04/12/2006	57	3,11	0	3	1	2	2	2	2	2	1	N	N	H	2	3	3B	3	0.6	5	1	2	Y	N	04/12/2006	06/12/2007	14	200	40	No
216	M	07/01/2007	47	1	0	4	1	2	2	1	1	1	1	N	N	H	1	1	2A	2	6.25	1	1	2	Y	Y	07/13/2007	11/06/2007	4	200	40	No
217	M	08/10/2010	61	2,3	0	2	1	2	2	2	1	2	1	N	N	NA	2	3	3B	3	8.2	2	3	3	Y	N	08/10/2010	05/13/2011	9	200	20	No
218	F	02/18/2006	55	8	0	6	2	2	2	1	2	1	1	N	N	N	1	1	2A	1	2.91	4	2	3	Y	N	02/18/2006	05/18/2006	3	100	20	y
219	F	04/08/2006	35	1,2,8	0	6	1	2	2	1	2	1	1	N	N	NA	2	3	3A	3	0	5	1	3	Y	Y	04/11/2006	03/13/2007	11	200	40	y
220	M	07/08/2005	51	1,2,6	0	6	1	2	2	2	1	1	1	N	N	H	2	3	3A	3	6.4	1	1	2	Y	Y	07/08/2005	12/08/2006	17	200	40	y
221	M	01/08/2006	66	1	0	2	1	2	2	1	1	1	1	N	N	H	1	3	2A	3	6.9	1	1	2	Y	Y	01/08/2006	08/28/2006	8	200	40	No
222	F	05/18/2005	58	1	0	6	1	2	2	1	2	1	0	N	N	NA	2	3	3A	3	2.97	2	3	3	Y	Y	05/18/2007	07/22/2008	14	100	40	y
223	M	05/31/2007	39	2,4,6,7	0	12	2	2	2	2	1	1	1	Y	N	H	1	3	3A	3	2.6	1	2	2	Y	Y	06/10/2007	08/19/2008	15	200	40	No
224	M	11/14/2006	51	1,8	0	6	1	2	2	1	2	1	1	N	H	H	2	1	2A	1	2.8	1	1	2	Y	Y	11/20/2006	03/29/2008	17	200	40	No
225	M	01/15/2010	62	2	0	2	2	2	2	1	3	1	1	N	NA	NA	1	1	3A	4	4.5	1	1	3	Y	Y	01/15/2010	09/23/2011	21	100	20	No
226	F	10/14/2008	51	1,2	0	6	1	2	2	1	2	1	1	N	N	N	1	1	3A	1	5.8	1	1	2	Y	Y	10/17/2008	06/02/2009	8	200	40	No
227	M	05/12/2006	53	14	0	1	1	2	2	1	1	1	1	N	N	N	2	4	2A	4	5.6	1	1	2	Y	Y	05/19/2006	04/04/2007	11	200	40	No
228	M	02/21/2006	56	8	0	2	1	2	2	1	2	1	0	N	N	N	1	4	2A	4	0.6	1	2	2	N	N	02/24/2006	05/21/2007	15	200	40	No
229	F	06/29/2009	50	9	0	1	2	2	2	1	2	1	1	Y	NA	NA	1	1	2A	1	0	5	1	2	Y	N	07/07/2009	10/04/2011	27	100	20	No
230	M	11/21/2007	63	3	0	5	2	2	2	1	2	1	0	N	NA	H	1	1	1A	1	Dec gam	5	1	2	Y	N	11/22/2007	02/28/2008	3	200	40	y
231	M	07/04/2008	57	2	0	2	2	2	2	1	2	1	1	N	N	H	2	3	3A	3	0	5	1	2	Y	Y	07/04/2008	12/09/2008	5	200	20	No
232	M	05/13/2008	54	2	0	2	1	2	2	2	1	1	1	N	NA	N	1	2	3A	2	2.2	2	1	3	Y	Y	05/20/2008	07/06/2009	14	150	20	No
233	M	02/20/2007	52	2	0	3	2	2	2	2	2	1	1	Y	NA	N	1	2	3A	2	4.5	4	1	3	Y	Y	02/24/2007	01/04/2008	10	200	20	y
234	F	02/26/2008	50	3	0	3	2	2	2	2	1	2	0	N	NA	H	1	3	1B	3	2.64	1	1	2	Y	N	02/29/2008	06/13/2008	4	200	20	No
235	M	04/29/2008	57	14	0	15	1	2	2	1	2	1	1	Y	N	N	1	1	2A	2	4.56	1	1	2	Y	Y	05/21/2008	01/21/2009	8	200	40	No
236	M	08/14/2008	50	1,2	0	2	2	2	2	1	2	1	0	N	N	NA	1	3	1A	3	4.23	2	1	2	Y	Y	08/29/2008	10/07/2008	1	200	20	No
237	M	10/01/2009	45	2,5	0	3	1	2	2	1	1	1	1	N	N	N	1	3	3A	3	11.7	1	2	2	Y	Y	10/01/2009	12/18/2009	3	100	20	No
238	F	07/16/2008	40	2	0	2	1	2	2	1	2	1	1	N	N	N	1	2	3A	2	3.2	1	2	3	Y	Y	08/05/2008	05/22/2009	10	200	20	No
239	F	07/05/2005	51	1	0	0.5	1	2	2	1	2	1	0	N	N	N	1	2	3A	2	0	5	1	2	N	N	07/05/2005	06/05/2006	11	200	40	y

240	M		03/15/2010		51	1,8,13	0	3	1	2	2	1	1	1	0	N	N	H	1	3	3A	3	9.2	1	2		1	y	y	04/13/2010	07/23/2010	3	200	20	No			
241	M		05/21/2010		52	2,3	0	1	1	2	2	1	1	2	1	N	N	H	1	3	3B	3	3.79	1	1		3	Y	Y	05/21/2010	09/07/2010	4	100	20	No			
242	M		11/23/2010		56	2	0	1	1	2	2	2	1	2	1	N	N	H	2	4	3B	4	10.72	1	1		2	Y	N	11/25/2010	03/29/2011	4	100	40	No			
CON	AE	TTR	RES	PD	TTP	ADDTt	STATUS	A/D/L	Last VISIT	2nd TT	Maint	START MAINT	STOP MAIN	Main Do	DVT	ABMT	TTT	Pre Tx	NOC	Mel	MUC	MNC	CD34	ANC1	ANC2	PL1	GCSF	Fever	ABD	PTS	PTPD	PTRD	PTM	PTMD	PTMDo			
0	0	na	NR	1	0	2	PD	2	11/19/2010	CTD	na	na	na	na	NO	1	19	PR	3	200	3	7.37	11.16	10	11	11	7	7	12	PR	Y	11/19/2010	0	0			
0	6	1	PR	1	3	2	PD	1	01/28/2010	DVD	c	na	na	na	NO	1	16	CRu	3	200	3	4.6	12.2	11	11	11	5	7	13	CRu	Y	01/28/2010	0	0			
0	0	1	PR	1	16	3	VGPR	1	11/15/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	1	PR	1	19	1	PD	2	12/30/2009	CP	b	07/04/2008	12/30/2008	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	1	PR	1	11	1	PR	1	12/22/2011	MPT	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	1	1	VGPR	1	4	1	PD	1	08/16/2011	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	1	PR	1	9	1	CRu	1	01/05/2012	PAD	b	04/29/2011	07/02/2011	100	NO	1	11	CR	2	200	3	7.71	7.3	12	12	11	5	3	12	CRu	N	01/05/2012	0	0	0		
0	0	1	PR	0	NA	NA	PR	1	02/02/2007	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	1	PR	0	NA	NA	PR	1	10/04/2005	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	1	CR	0	NA	NA	CRu	1	04/20/2011	na	a	na	na	na	NO	1	9	CR	1	200	3	5.4	2.2	12	12	12	6	6	11	CRu	N	04/20/2011	0	0			
0	0	1	CRu	0	NA	NA	CRu	1	07/29/2011	na	b	02/01/2011	07/27/2011	150	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	2	PR	1	12	2	PD	2	02/20/2009	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	2	PR	1	42	1	PR	1	10/21/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
1	0	2	PR	1	14	1	PD	1	12/29/2011	CTD	b	05/27/2011	12/16/2011	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	1	2	PR	1	17	1	PD	2	10/17/2008	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	3	2	PR	1	10	1	PD	2	06/27/2008	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	na	NR	1	0	2	VGPR	1	12/02/2011	LLD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
1	0	2	PR	1	9	1	PR	1	09/09/2011	MPT	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
1	0	2	PR	1	6	1	CRu	1	12/21/2006	PAD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
0	0	2	PR	0	NA	NA	PR	1	01/23/2009	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
1	0	na	NR	1	0	2	PD	2	06/30/2010	MPT	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na			
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0	0	4	PR	0	NA	NA	PR	1	08/06/2010	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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1	0	na	NR	1	0	1	PR	1	11/01/2011	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	na	NR	1	0	1	PR	1	12/13/2011	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	3	PR	1	7	3	PR	1	10/14/20	CTD	c	na	na	na	N	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na

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0	1	5	CRu	1	38	1	PD	2	12/02/2008	CTD	b	02/03/2006	10/24/2008	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	5	PR	0	NA	NA	CR	1	12/28/2011	na	a	na	na	na	NO	1	9	VGPR	1	200	3	5.4	9.9	10	11	11	5	1	5	CR	N	12/28/2011	1	6	100		
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0	0	3	VGPR	1	43	1	PR	1	12/19/2011	CTD	b	03/11/2008	09/09/2008	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	6	PR	1	33	2	PD	2	01/22/2011	PAD	a	na	na	na	NO	1	16	PR	2	140	2	7.3	3.03	12	12	12	6	3	16	VGPR	Y	06/14/2010	2	16	na		
0	0	3	VGPR	1	6	1	PD	2	10/19/2009	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	0	6	PR	1	6	1	PR	1	12/16/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na

0	0	3	VGPR	1	11	1	PD	2	10/06/2009	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	6	PR	1	6	1	PR	1	09/30/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	0	3	VGPR	1	13	1	PR	1	08/14/2009	CTD	b	03/10/2009	05/26/2009	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	6	PR	1	6	1	PD	1	06/09/2010	CTD	c	na	na	na	y	1	16	VGPR	2	180	2	2.78	6.3	10	10	10	6	2	7	VGPR	Y	1/7/2008	1	9	100		
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0	0	na	NR	1	0	1	VGPR	1	07/18/2011	PAD	na	na	na	na	NO	1	26	CR	2	200	3	6.12	4.47	11	11	12	5	1	8	CRu	N	07/18/2011	0	0			
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0	0	6	PR	1	11	1	PD	1	09/14/2011	CTD	c	na	na	na	NO	1	30	VGPR	2	200	3	6.1	2.68	12	12	21	7	3	10	PR	Y	09/14/2011	0	0			
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0	0	6	PR	1	10	1	VGPR	1	01/03/2012	CTD	b	02/02/2010	01/03/2012	200	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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LTF	LTF	na	LTF	LTF	LTF	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
LTF	LTF	na	LTF	LTU	LTU	LTF	LTF	LTF	LTF	na	na	na	na	na	LTF	LTF	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	na	NR	1	0	NA	PD	2	03/07/2008	na	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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1	0	3	PR	0	NA	NA	PR	1	11/08/2011	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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1	5	7	PR	1	12	3	PR	1	01/24/2012	HDD	b	07/12/2004	03/04/2005	200	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	7	PR	1	8	1	PR	1	08/06/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	8	PR	1	8	1	VGPR	1	10/03/2007	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	3	VGPR	0	NA	NA	CR	1	12/16/2011	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	8	VGPR	1	10	1	PD	2	09/21/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na

1	0	3	VGPR	0	NA	NA	VGPR	1	04/18/2008	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	1	8	PR	0	NA	NA	VGPR	1	05/31/2011	na	b	11/14/2006	05/31/2011	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	3	VGPR	0	NA	NA	VGPR	1	05/09/2008	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	8	VGPR	0	NA	NA	CRu	1	09/04/2009	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	1	3	VGPR	0	NA	NA	VGPR	1	10/04/2011	na	b	08/08/2008	11/14/2008	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	8	VGPR	0	NA	NA	CR	1	06/12/2009	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	0	3	CR	0	NA	NA	CR	1	08/09/2011	na	b	05/01/2007	01/27/2009	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	3	CR	0	NA	NA	VGPR	1	07/19/2011	na	b	04/04/2008	08/26/2008	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	9	VGPR	1	28	1	PD	1	07/29/2011	TD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	0	3	CRu	0	NA	NA	CRu	1	11/04/2011	na	b	12/10/2010	11/04/2011	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
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0	1	4	PR	1	15	2	PR	1	04/16/2010	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	13	PR	0	NA	NA	PR	1	06/12/2007	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	1	4	PR	1	4	2	PR	1	07/17/2008	LD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	0	13	VGPR	0	NA	NA	VGPR	1	05/13/2011	na	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	PR	1	46	2	PR	1	11/17/2011	MP	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	PR	1	11	3	PD	1	06/21/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	PR	1	14	3	PR	1	12/23/20	CTD	c	na	na	na	N	1	9	PR	3	20	4	8.1	9.1	10	10	11	6	2	16	PR	Y	10/4/2	1	24	100

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0	0	4	PR	1	14	3	PD	2	01/17/2009	CTD	b	08/29/2006	03/06/2007	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	4	4	VGPR	1	27	3	PR	1	09/02/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	VGPR	1	11	3	PD	2	03/23/2010	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	VGPR	1	51	3	PD	2	11/27/2011	TD	a	na	na	na	NO	1	15	PR	1	200	2	8	7.2	11	11	8	5	5	11	Cru	Y	02/01/2011	1	10	200
0	0	4	CRu	1	21	1	PD	1	09/25/2011	CP	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	PR	1	8	1	VGPR	1	12/02/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	PR	1	11	1	PD	1	04/05/2007	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	PR	1	47	1	PD	2	12/17/2010	CTD	b	11/03/2006	01/08/2010	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	1	4	PR	1	27	1	PR	1	10/04/2011	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	na	NR	1	0	2	PD	1	05/15/2009	CP	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	5	na	PD	1	0	2	PR	1	11/04/2011	CP	na	na	na	na	y	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	4	VGPR	1	14	1	VGPR	1	11/17/2009	CTD	c	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	0	4	VGPR	1	25	1	PD	1	03/24/2009	CTD	b	01/04/2008	03/13/2009	100	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	1	na	MR	1	0	2	PR	1	05/10/2011	CTD	na	na	na	na	y	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	0	na	MR	1	0	2	PD	2	09/29/2009	CTD	na	na	na	na	y	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	na	NR	1	0	2	VGPR	1	09/29/2011	CTD	na	na	na	na	NO	1	14	VGPR	3	200	3	19.64	3.01	10	10	9	4	1	5	CRu	N	09/29/2011	2	7	na
0	0	na	NR	1	0	2	PR	1	12/27/2011	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	na	NR	1	0	2	VGPR	1	02/01/2011	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
1	0	na	NR	1	0	2	PD	2	07/17/2007	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	na	NR	1	0	2	PD	2	10/26/2010	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	na	NR	1	0	2	PD	1	05/20/2011	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
0	0	na	NR	1	0	2	PR	1	01/09/2012	CTD	na	na	na	na	NO	0	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na